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RESPIRATORY KYMOGRAPHY IN SILICOSIS

by

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The diagnosis of silicosis will demand a careful assessment of the amount of work the patient is able to perform and this may be said to bear a direct relationship to the capacity of the lungs. This capacity will be reduced by any decrease in the functioning alveolar space in the areas of the lungs affected. During the entire course of the disease and specially during the fibrotic stage with severe shrinkage, the densities are generally localized to the upper zones of the lungs. Breathing will consequently become more and more dependent on the lower parts of the lungs and the diaphragm will gradually take over the main part of the respiration. At the same time, secondary emphysema in the basal zones will further decrease the respiratory capacity.

A study of the diaphragmatic and costal movements is important in the assessment of the breathing capacity. Fluoroscopy can give a general idea of the excursions of the diaphragm but by means of roentgen kymography it is possible to obtain an objective record of the respiratory movements of both the diaphragm and ribs.

The literature on roentgen kymography in silicosis is scanty. DI LAURO & DI GUGLIELMO (1950) reported 12 cases in which they investigated the morphology, symmetry and synchronism of the diaphragmatic movements, as well as the synchronism of the diaphragmatic in relation to the costal movement

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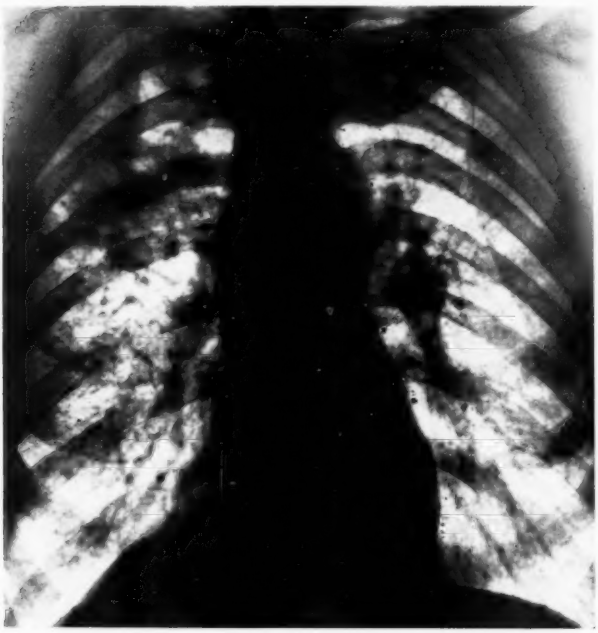


Fig. 1. Lungs, silicosis stage III. Asymmetric distribution of densities. Confluent infiltrations in upper zone of right lung; emphysema, flattened diaphragm.

They noticed no abnormality regarding these points and made no mention of the amplitude of the diaphragmatic or costal movements. NAUMOW (1959) published roentgenkymographic studies in pneumoconiosis without illustrations and found no direct relationship between the morphologic appearances and changes in function. In his opinion dysfunction of the respiration, as shown by protracted expiration and deformation of the diaphragmatic waves, was caused by tuberculosis, and not by pneumoconiosis. His conclusion was that roentgen kymography cannot be considered a useful method in the early diagnosis of pneumoconiosis.

We present a series of cases of silicosis, diagnosed clinically and roentgenologically and examined by roentgen kymography of the respiratory movements of the diaphragm and ribs.

Material and Methods. The material comprises 25 cases examined with the kymographic technique described by SCHMIDT (1960). Of these, 4 cases were classified as stage I, 4 as stage II and 17 as stage III of silicosis. In the last

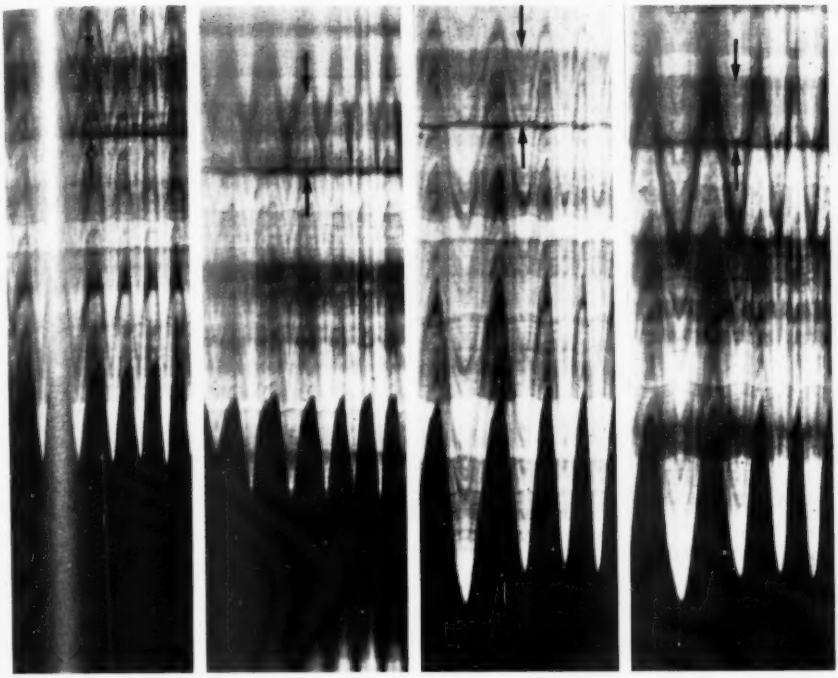


Fig. 2. Same case as in fig. 1. Kymography of diaphragm and ribs in ordinary (a) and deep (b) respiration. Normal waveform. Normal amplitude of diaphragmatic waves. Markedly reduced amplitude of costal waves (arrows).

group two of the cases had active and two inactive tuberculosis associated with the silicosis.

The kymographic examination was performed in the supine position. The kymograph contains two movable lead plates with a 1 mm wide and 50 cm long slit in each. Each slit is placed under fluoroscopic control over one side of the diaphragm and lower part of the chest, about 2 to 4 cm medial to the lateral thoracic wall and parallel to the long axis of the body. Two 30 × 40 cm films are placed in the moving tray and exposed, one during ordinary and one during deep respiration. The exposure time is 20 seconds. We obtain a record of the movement of a one millimetre broad segment of the diaphragm and the lower part of the chest on each side. The posterior parts of the 7th to the 10th ribs are usually recorded. The movements of the anterior parts of the

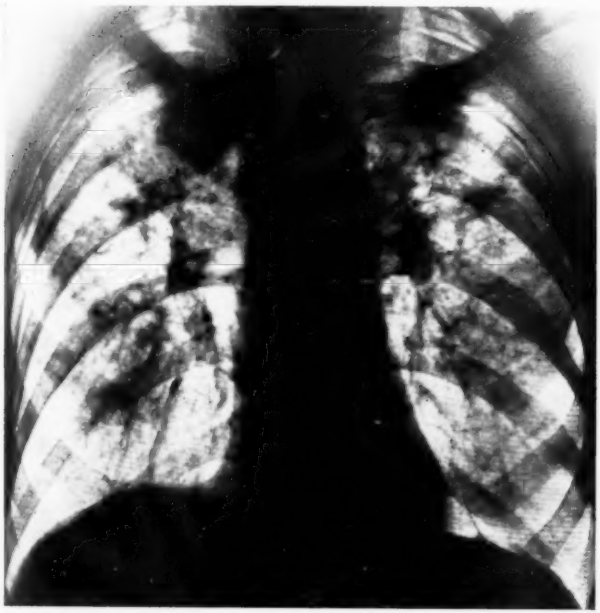


Fig. 3. Lungs, silicosis stage III. Fairly symmetric distribution of densities. Confluent infiltrations in upper medial parts of lungs; shrinkage and emphysema. The diaphragm is slightly flattened.

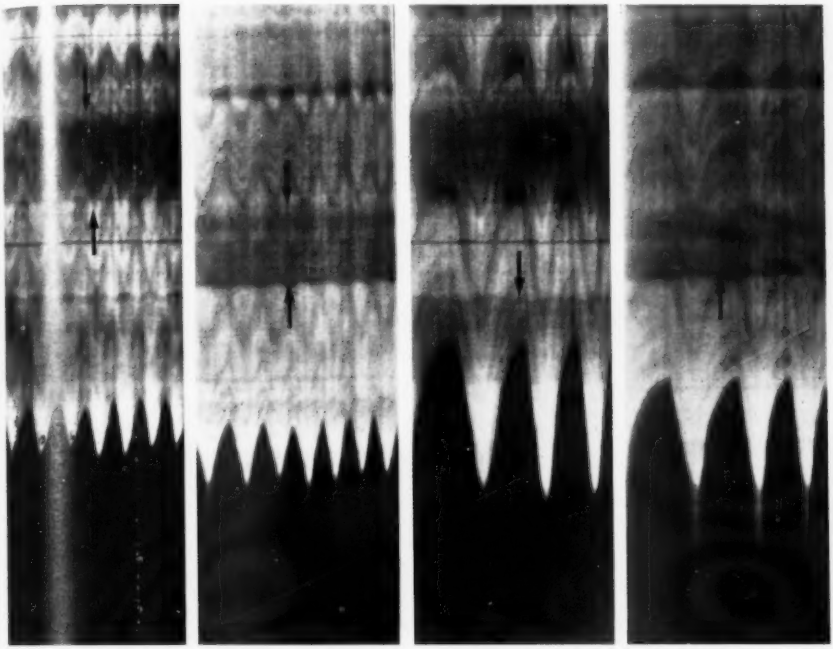
ribs are usually not recorded and the description of the costal movements in this paper therefore refers to the posterior parts of the ribs.

The normal kymographic tracing of the diaphragmatic movements is a regular, slightly asymmetric, steep wave. The ascending limb corresponds to expiration, the descending one to inspiration. The asymmetry is caused by a slight retardation of the movement near the end of expiration. The average amplitude in normal cases is 2 cm in ordinary, and 4.5 cm in deep breathing.

The normal kymographic tracing of the costal movements is a regular and slightly asymmetric but flat wave, whose direction is opposite to that of the diaphragmatic wave. Thus the descending limb corresponds to expiration, the ascending one to inspiration. The average amplitude in normal cases is 1 to 2 mm in ordinary, and 3 to 5 mm in deep breathing.

Results

The form of the diaphragmatic waves in the kymogram was normal in 18 cases (Figs 1 to 4). The form was abnormal during expiration due to



(right) a (left) (right) b (left)

Fig. 4. Same case as in fig. 3. Kymography of diaphragm and ribs in ordinary (a) and deep (b) respiration. Normal waveform. Slightly reduced amplitude of diaphragmatic waves. Very small amplitude of costal waves (arrows).

more small inspiratory movements unilaterally in 4 cases (Figs 5 and 6), and bilaterally in 3 cases. These last 7 cases belonged to stage III group.

The amplitude of the diaphragmatic waves was within normal limits in 8 cases (Figs 1 and 2), increased in 9 (Figs 5, 6, 7 and 8), and reduced in 8 cases (Figs 3 and 4). In 6 of these last 8 cases, with exception of the one illustrated the difference of amplitudes in ordinary and deep respiration was small, and in the two remaining cases there was no difference. Disturbances in the respiratory diaphragmatic amplitude occurred in all stages of the disease. As many as 11 of the 17 cases belonging to stage III had ordinary or increased diaphragmatic amplitudes.

A difference of amplitude between right and left sides was observed in some cases (Figs 3, 4, 7 and 8); this difference did not exceed 0.5 cm, which is a normal finding. There was no correlation between the differences in amplitude on the right and left sides and differences in the radiologic appearances of

Fig. 5. Lungs, silicosis stage III. Fairly symmetric distribution of densities. Shrinkage in upper and middle zones on both sides; emphysema. Diaphragm normal.

both lungs, when present. No paradoxical movements of the diaphragm were observed.

The form of the costal waves is generally difficult to assess due to the small amplitude and superimposed structures. In all probability the abnormal wave form in the diaphragmatic tracing which occurred in some cases was represented in the costal tracing but, with one exception (Figs 5 and 6), was too small to be discernible.

The amplitude of the costal movements was average in 7 cases (Figs 7 and 8), increased on one side in 2, and reduced in 8 cases (Figs 1, 2, 3 and 4). No appreciable costal respiration was evident on either side in 4 cases or on one side in another 4 cases (Figs 5 and 6). In one of the seven cases with average amplitude the costal movements were paradoxical; for this we have no satisfactory explanation.

There was no constant relationship between the disturbances in the diaphragmatic and costal movements and the various stages of silicosis. It may also be noted that there was no appreciable difference observed in the wave

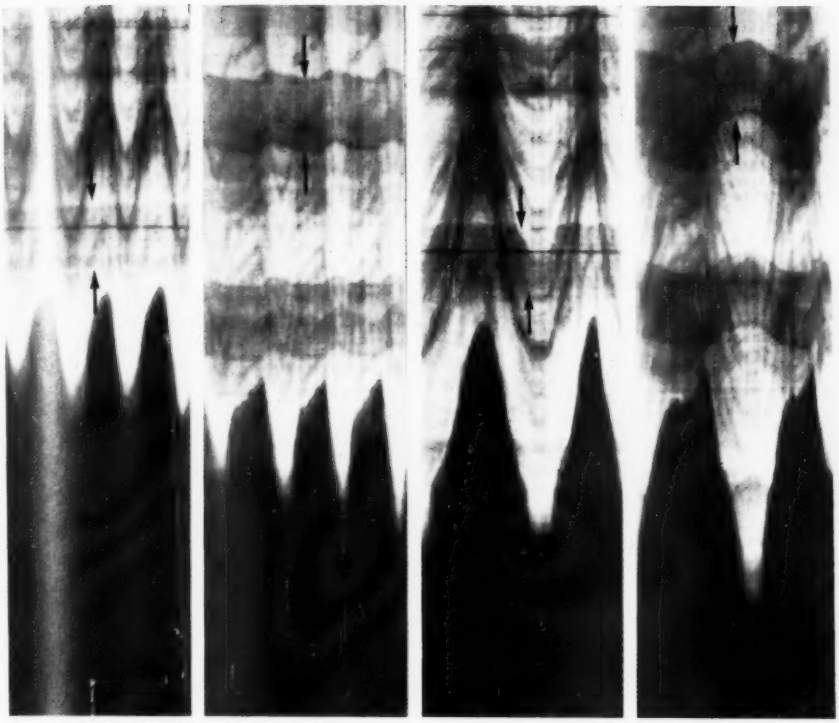


Fig. 6. Same case as in fig. 5. Kymography of diaphragm and ribs in ordinary (a) and deep (b) respiration. Normal diaphragmatic waveform on right side. Small inspiratory movements at the end of expiration on the left side. Amplitude of diaphragmatic waves moderately increased in deep respiration. No costal movements on right side, normal amplitude on left side (arrows).

form or amplitude between the 4 cases which had tuberculosis associated with silicosis and the other cases.

Discussion and conclusions

The three different stages of silicosis are represented in our series of 25 cases. The majority were classified as stage III and about half of these had advanced fibrotic changes.

According to the results the silicotic changes in the lungs in the majority of the cases did not influence the form of the kymographic waves of the diaphragm and ribs. A minority of the cases had a slightly irregular expiration

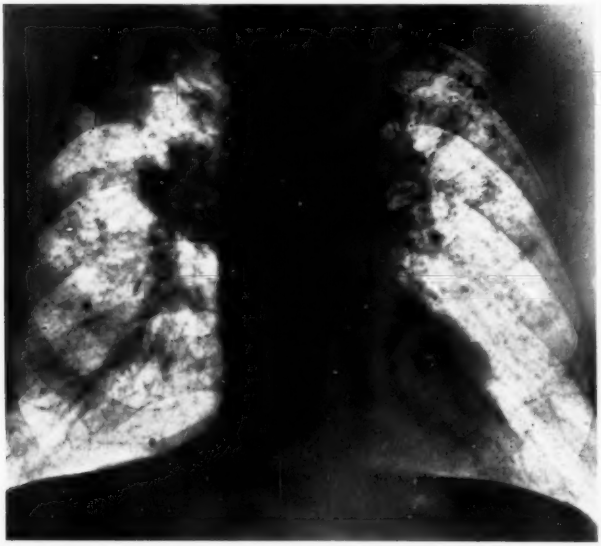


Fig. 7. Lungs, silicosis stage III.[1] Asymmetric distribution of densities. Confluent infiltrations in upper lateral part of right lung. Shrinkage and emphysema, flattened diaphragm.

phase. This is in no way a characteristic finding in silicosis as it also occurs in other pulmonary conditions. This indicates that lung changes due to silicosis do not generally affect the form of the breathing mechanism.

The amplitude of the diaphragmatic respiratory movements was average or increased in nearly three quarters of the cases, and moderately reduced in the rest. This shows that the diaphragmatic function is usually not impaired in silicosis, even when advanced pulmonary changes are present. On the contrary, the relatively large number of cases with increased diaphragmatic amplitude would suggest that a compensatory mechanism for the reduced respiratory capacity of the damaged lung tissues often develops. It also suggests that the emphysematous component of the functioning part of the lungs is not very large, as the pulmonary tissues are capable of great volume changes. When the amplitude was reduced this, with a few exceptions, occurred only in deep respiration and was of moderate degree.

In some of the cases the diaphragm was more or less flattened without constant relationship to its amplitude. This change in the shape of the diaphragm does not therefore in itself indicate impairment of the movements.

The amplitude of the costal movements was in the majority of the cases reduced or absent. The impaired costal respiration may be explained by the

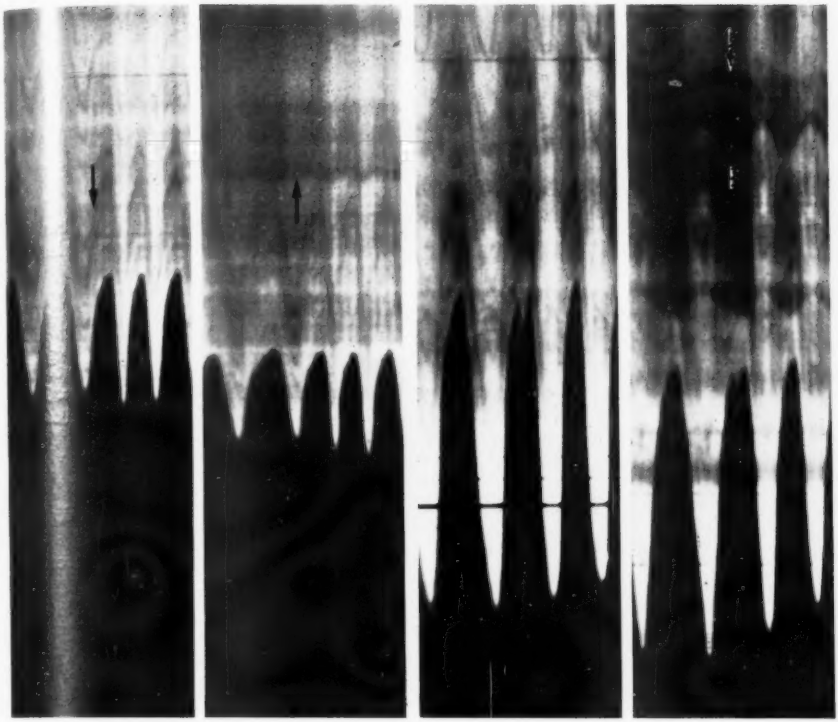


Fig. 8. Same case as in fig. 7. Kymography of diaphragm and ribs in ordinary (a) and deep (b) respiration. Abnormal form of occasional waves due to small inspiratory movements at the end of deep expiration. Markedly increased amplitude of diaphragmatic waves in deep respiration. Normal amplitude of costal waves (arrows).

reduction of the respiratory capacity in the upper parts of the thorax due to the fibrotic changes; these parts of the lungs, normally ventilated mainly by costal movements, were therefore more or less not functioning. The deficient costal respiration was compensated by the diaphragmatic respiration. This would confirm the relationship between costal and diaphragmatic breathing in the compensatory mechanism.

It would appear that respiratory kymography may be used as a qualitative functional test for evaluation of the respiratory capacity of a patient. Moreover, it may also be valuable from the therapeutic point of view. As in emphysema due to other causes, the treatment of emphysema in silicosis with respiratory exercises varies with the individual type of respiratory deficiency. The result of treatment may also be followed by means of kymography.

SUMMARY

Respiratory kymography was used for studying the diaphragmatic and costal mov ents in a series of 25 cases of silicosis representing all three stages. The use of the meth as a qualitative test of respiratory capacity is discussed.

ZUSAMMENFASSUNG

Die respiratorische Kymographie wurde in 25 Fällen mit Silikosen aller 3 Stadien b utzt, um diaphragmatische und kostale Bewegungen zu studieren. Die Anwendung der M thode als qualitativer Test der Respirationskapazität wird besprochen.

RÉSUMÉ

Sur une série de 25 cas de silicose représentant les trois stades, les auteurs ont u isé la kymographie respiratoire pour étudier les mouvements du diaphragme et des côtes. L'utilisation de cette méthode comme test qualitatif de la capacité respiratoire est discu e.

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TRANSVERSAL TOMOGRAPHY OF THE DESCENDING AORTA

by

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The posterior mediastinum is a region not readily accessible to roentgen investigation. The demonstration of the various organs contained in the posterior mediastinum call for the employment of techniques which may include conventional roentgenography of the chest, contrast roentgenography of the oesophagus, and angiography (for example, thoracic aortography). Examination of the oesophagus involves little discomfort to the patient. Detailed assessment of the descending aorta, however, requires the much more complicated and often trying procedure of thoracic aortography. Although admittedly it is often possible to establish the position of the left margin of the descending aorta in the conventional film, the position of the right border and therefore the width of this structure cannot usually be determined, except at its uppermost part. Transversal tomography should provide further information about the descending aorta and its width. It forms the subject of this communication.

In assessing transversal tomograms particular regard must be paid to the errors inherent in the method and dependent upon the morphologic features of the region examined. The inherent disadvantages of the method consist mainly in the appearance of blurred outlines of large and dense structures near to the actual layer and in deformation of the image. The blurred outlines particularly affect smaller, less opaque structures, but they are easily re-

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cognized and can be partly eliminated by a good technique, i. e. the use of adequately penetrating rays and contrasty films. The deformation of the image that sometimes occurs has been analysed by BONTE et coll. (1955), OLIVA et coll. (1957), and others, who found it to be determined by the mutual relationship of the site, size and absorption density of the object. It occurs when the object, during rotation, is struck by the image-forming beam only in certain sectors, and is being masked by other, more opaque structures during other phases of rotation.

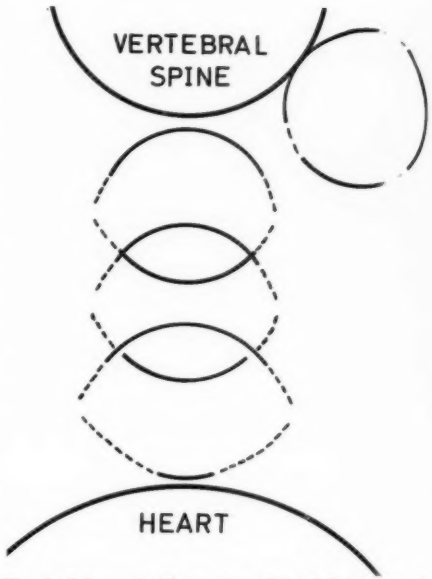


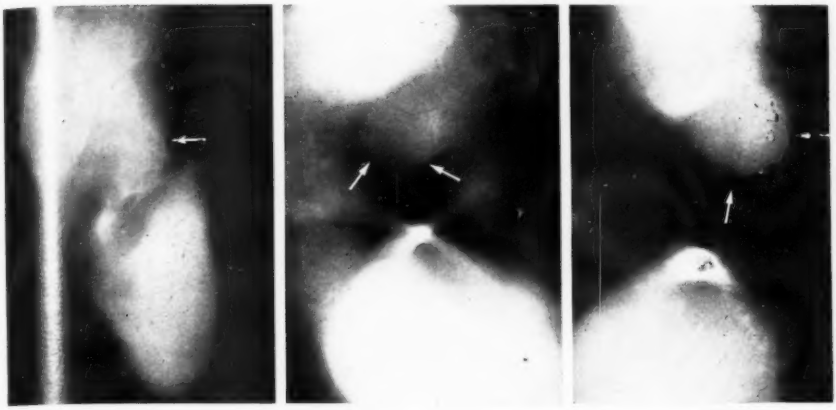
Fig. 1. Schematic illustration of the deformation of a cylindrical object (aorta) in the posterior mediastinum. The varying degree of deformation depends on the position of the object in relation to other organs such as the heart and vertebral column. The ideal position of the aorta is to the left of the vertebral spine. Sharp contour ———, unsharp contour — — —.

The morphologic features of the region in question are highly significant in this connection. From the point of view of transversal tomography the conditions in the posterior mediastinum are particularly difficult, because the structures are bounded posteriorly by the vertebral column and anteriorly by the heart, both of which are dense; the heart in particular is of a considerable size. These features impair the visibility of the posterior mediastinal structures, since the demonstration of these structures chiefly depends on the amount of primary tangential (i. e. contour-forming) beam. An unfortunate combination of the tomographic disadvantages and anatomical conditions may even lead to failure in demonstrating certain structures if the directly tangential beam is insufficient.

The conditions for the use of transversal tomography in the diagnosis of mediastinal hernia were discussed in an earlier paper (LODIN 1957) in connection with model experiments in reproducing linear structures. The present investigation is concerned with the representation of cylindrical structures (such as the aorta) in model experiments, the results being compared with the findings in clinical roentgen examinations.

Experiments with the model thorax

A model thorax made of 'plexiglas' (LODIN 1957) was used. Plexiglas cylinders of varying diameter representing the aorta were placed in the posterior mediastinum



a b c

Fig. 2. Three variations in the demonstration of the aorta in transversal tomography. a) Shallow posterior mediastinum. Only the left border of aorta (arrow) is clearly visible. Shape and width of aorta not demonstrated. b) Deep posterior mediastinum. Aorta (arrow) visible in front of the vertebrae. The circumference appears oval with the long axis in the frontal plane and is obviously deformed by the heart and vertebral column. c) Deep posterior mediastinum. Aorta (arrow) in close relation to the left side of the vertebrae, is well defined, except where in contact with spine. Slight deformation.

tinum. The experiments were carried out with the aid of a Pantix Strator (Zuder, Genoa) under the same exposure conditions as in clinical investigations. The focus-object-distance was about 250 cm, and the object-film-distance about 50 cm, the angle of incidence being 25°. Ordinary cassettes with double screens and without grid were used.

The experiments with the model thorax were intended to elucidate the importance of the heart-spine distance as well as the width of the aorta and its position in relation to the heart and vertebral column in the formation of the image in transversal tomography. In the experiments therefore, the heart-spine distance and the thickness and position of the plexiglas aorta were varied. The findings may be summarized as follows.

1. The greater the heart-spine distance the less the deformation and larger will be the part of the circumference of the cylinder (aorta) that will be sharply shown; as the distance increases, the sector of rotation during which primary tangential rays strike the aorta becomes larger.

2. If the aorta is situated in the midline the deformation is less the closer the aorta is to the spine (Fig. 1). The possibility of its clear demonstration is chiefly determined by the nearest organ, in this case the vertebral column. Due to the smaller volume of this structure, the sector in which the aorta is struck by tangential rays increases.

Fig. 3. Transversal tomogram at the level of the hila. The descending aorta is not visible.

3. The more lateral the aorta is situated the less will be the deformation. (Fig. 1). Deformation is least when the aorta lies lateral to the left-hand margin of the vertebral column. The more lateral the aorta is situated in the mediastinum the less of it will be masked by the vertebral column and heart at the same time. Finally, when the aorta is lateral to the vertebrae, it can be masked by either the vertebral column or the heart only during a certain phase of rotation.

4. The greater the diameter of the cylinder (aorta) in relation to the heart and vertebral column the better will it be shown. If the aorta is narrow in relation to these organs, and at the same time situated in the midline, there is a risk that it may not be seen at all, owing to lack of contrast and the predominance of faint outlines of other structures.

Clinical features

The position of the descending aorta varies, but as a rule this organ is situated in close relation to the anterior or lateral aspect of the left-hand side of the thoracic vertebrae. The aorta may lie very much more medial, however, and

may even make no contact with the vertebral column but lie free in the posterior mediastinum. Finally, the relation of the descending aorta to the vertebral column may vary at different levels in one and the same patient.

In applying the results of the model experiments to clinical roentgenology therefore, it must be borne in mind that conditions will vary from case to case and even within the individual chest. The experiments do, however, show that the demonstration of the aorta is favoured when this organ is situated laterally, as it usually is.

In principle, the clinical and experimental findings tally. The demonstration of the aorta was better throughout in the model experiments, however, probably because of the 'purer' conditions, no regard having been paid to the other organs and soft parts in the mediastinum (for example, the oesophagus) which may be continuous with the aorta and reduce its contrast. The vertebral column in the living subject was also denser than that in the model.

As can be seen from Fig. 2, demonstration of the aorta is favoured by a deep mediastinum in which the vessel is situated lateral to and contiguous with the thoracic vertebrae. In order to obtain a fairly accurate assessment of the size of the aorta two diameters at right angles to each other should if possible be measured. The whole circumference of the vessel is seldom shown although some part is usually visible and an impression can generally be gained of more than half of it. Cases do occur, however, in which the aorta cannot be seen at all (Fig. 3).

Conclusion

Transversal tomography only exceptionally gives a true impression of the transverse section of the thoracic aorta. The chances of demonstrating the size of the vessel are best in subjects in whom the mediastinum is deep, for example patients with scoliosis or emphysema. Demonstration of the vessel is also favoured if the subject takes a deep breath, thus increasing the heart-spine distance and accentuating the difference in contrast between the aorta and lung. The large, dense adjacent organs, the heart and vertebral column, are responsible for the unfavourable conditions.

It is clear from this study that the outlook for improving our knowledge of the descending aorta with the aid of transversal tomography is limited.

SUMMARY

The requirements for the demonstration of a cylindrical object in the posterior mediastinum by transversal tomography are examined in experiments using a model thorax of plexiglas. The results are correlated to those of clinical investigations. It is evident that deformation of the object greatly limits the value of transversal tomography in the examination of the descending aorta.

ZUSAMMENFASSUNG

Die für die Demonstration eines zylindrischen Objektes im hinteren Mediastin[um] bei transversaler Tomographie notwendigen Bedingungen sind mit Hilfe eines Thoraxmod[ells] aus Plexiglas experimentell untersucht worden. Die Resultate werden mit denen klinischer [Unter]suchungen verglichen. Es ist offenbar, dass die Deformierung des Gegenstandes, die [bei] der transversalen Tomographie auftritt, den Wert der Methode für die Untersuchung de[r Aorta] descendens in grossem Ausmasse begrenzt.

RÉSUMÉ

Sur un modèle de thorax en plexiglas, l'auteur a étudié les conditions permettant d[e mettre] en évidence, par tomographie transverse, un objet cylindrique dans le médiastin pos[térieur.] Il compare ces résultats avec ceux des examens cliniques et il montre que la déforma[tion de] l'objet diminue beaucoup l'intérêt de la tomographie transverse pour l'examen de [l'aorte] descendante.

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CERVICAL MYELOGRAPHY WITH A WATER-SOLUBLE CONTRAST MEDIUM

An experimental study in dogs

by

BERIT FUNKQUIST

Subarachnoid myelography may be performed both with positive contrast media such as iodized oils (Lipiodol®, Pantopaque®), or water-soluble contrast media (Abrodil®, Kontrast U®), as well as with negative contrast media (air, oxygen). The use of the comparatively rapidly resorbed water-soluble Abrodil has been confined to the lumbar region; this is because of its irritant properties, which have been considered to necessitate previous spinal anaesthesia. The iodized oils, on the contrary, have been used for cervical myelography. They have, however, in addition to the late complications (e. g. subarachnoid granuloma) caused by their slow resorption, the drawback of being unevenly distributed and apt to be broken down into droplets (e. g. LINDGREN 1954). After lumbar injection, which may be required when suboccipital puncture is contraindicated, the oil is transported only with difficulty to the cervical region (JIROUT 1958).

Air, as opposed to the iodized oils, is rapidly resorbed, and has no serious irritant effect on the membranes of the spinal cord. This contrast medium is therefore generally used for myelography of the cervical region in man (LINDGREN 1939, ODÉN 1953, MURTAGH et coll. 1955, JAKOBSEN 1956, JIROUT 1958). On the other hand, the gaseous contrast media do not permit such a detailed study of the subarachnoid space and the root sheaths of the spinal nerves as does a positive contrast medium, particularly one that is water-soluble.

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It has been shown that water-soluble contrast media may be used f the roentgenologic examination of the thoracic part of the subarachnoid sp e in the dog (FUNKQUIST & OBEL 1960). In these experiments a contrast m lium to which Xylocaine had been added was injected, without previous inal anaesthesia, into the lumbar region under light anaesthesia and succinylc oline relaxation, with artificial respiration. An account is given in the present aper of a study on the possibilities of extending the use of water-soluble c trast media to the examination of the cervical part of the subarachnoid spac

Three possibilities exist for myelographic depiction of the cervical sub achnoid space with a water-soluble contrast medium.

1. The medium is injected suboccipitally, with the forequarters of the a imal elevated.

2. The medium is injected lumbarly, with the forequarters of the a imal elevated, in such doses that it is forced up to the desired level of the c vical spine.

3. The medium is injected lumbarly, with the hindquarters of the a imal elevated, and is allowed to run of its own accord into the cervical subarac noid space.

In preliminary experiments the first alternative was found to involve a great risk of the highly concentrated medium penetrating into the intracranial part of the subarachnoid space and causing disturbances in function of the central nervous system.

The second alternative implies that the whole of the spinal subarachnoid space must be filled with contrast medium. The safety margin against damage to the spinal cord by contrast medium has, however, proved to be small on injection of such large quantities (FUNKQUIST & OBEL 1961).

In view of the aforegoing considerations, my experiments on cervical myelography with a water-soluble contrast medium have been based on the third alternative, i. e. lumbar subarachnoid injection with the hindquarters of the animal elevated.

I. Experiments in dogs without spinal cord compression

Most of the dogs were aged 6 months to 1 year, and weighed from 5 to 20 kg. Before the experiment, some of them showed signs of an infectious disease (canine distemper or infectious hepatitis). In certain experiments, the same dog was given two injections of contrast medium, either at an interval of about 1 hour (without interruption of anaesthesia), or at an interval of 14 days.

Technical details. With the dog under Pentothal-nitrous oxide anaesthesia, the subarachnoid space was punctured lumbarly (FUNKQUIST 1961), and in certain cases suboccipitally as well (BROOK 1936). Anaesthesia and ventilation were then maintained by artificial respiration with a 4: 1 mixture of nitrous oxide and oxygen (Pulmomat, Dräger). Complete muscle relaxation was induced and maintained throughout anaesthesia by repeated i. v. injections of suc-

cinyl oline iodide (Celocurin®), in doses of about 0.5 mg/kg bodyweight. The contrast medi consisted of Kontrast U® 20 % with the addition of 1 mg/ml Xylocaine hydrochlor (FUNKQUIST & OBEL 1960). In some experiments, methylene blue was added to the contr solution. This made it possible to determine post mortem which parts of the subarach id space had been in contact with the solution.

Wi the animal in the right lateral position or prone position and with the hindquarters eleva to about 45°, the contrast medium was injected lumbarly in a dose of 0.3 ml/kg bodyweigl Unless otherwise stated, the medium was injected during 10 sec. In 7 experiments in all, ti position of the lumbar needle in the subarachnoid space was doubtful; in these cases, a test jection of 0.5 ml of contrast medium of the aforementioned composition was given 10 to 20 in before the main injection. The experimental conditions were varied as regards the suboc ital withdrawal of spinal fluid before the injection of contrast medium, position of the an nal (lateral or prone), position of the head and neck during and after the injection, and d ation of elevation of the hindquarters.

In ne of the experiments in which lumbar injection of contrast medium was preceded by suboc ital spinal tap, the spinal fluid flowing from the suboccipital needle after injection of con ast medium was examined for the presence of iodine by the following rough, rapid metho . One drop of spinal fluid was placed every 15 to 30 sec on a cautery wire that had been h ated until it was red-hot. It was then placed underneath and about 1 cm from a filter paper moistened with 1 % starch solution. Tests were made with a mixture of spinal fluid and contrast medium, the concentration of the latter being known. It was found that the filter paper consistently assumed a blue colour within a few seconds when the concentration of the medium was 1 % or over.

Roentgenograms of the cervical and anterior part of the thoracic region were taken immediately after the injection of contrast medium and, as a rule, every 30 sec during the first minutes following it. In the experiments in which the hindquarters were elevated for some time, the roentgenograms were obtained at longer and varying intervals during the later part of this period. The majority of the projections were in the lateral plane. The direction of the rays was at right angles to the examining table when the animal was in the lateral position, and horizontal when it was in the prone position. In some cases, the lateral films were followed by frontal views after the animal had been rotated 90°.

When the roentgenologic examination of the cervical spine was completed, the forequarters of the animal were elevated to about 25°. Films were then obtained of the lumbar spine, to rule out epidural injection. In certain cases, roentgenograms of the cervical spine were also taken after elevation of the forequarters. The animal was kept in this position until it showed signs of waking; this was generally 20 to 40 min after injection of the contrast medium. It was then placed with the trunk in the horizontal position with the neck and head slightly raised by a pillow. It was allowed to remain in this position until it made spontaneous attempts to get up.

In most experiments, the pressure in the femoral artery was recorded by the method of HANSSON & OBEL (1958).

The experimental conditions were varied as follows:

A. Lumbar injection of contrast medium without preceding spinal tap, head and neck extended during injection

After lumbar puncture of the subarachnoid space, the hindquarters of the animal were elevated. With the animal in the lateral position, the mixture of contrast medium and Xylocaine was then injected through the puncture needle without preceding drainage of spinal fluid.

Number of animals and observation period: Three. Two of these 3 dogs were used, about 1 hour later, for further experiments, during which 1 of them was killed. The other 2 dogs were kept under observation for 2 months after the experiment.

Duration of elevation of hindquarters: About 4.5 min in every experiment.

B. *Lumbar injection of contrast medium with preceding suboccipital spinal tap, head and neck extended during injection*

After lumbar puncture of the subarachnoid space, the hindquarters of the dog were raised. Following suboccipital puncture the spinal fluid was withdrawn as completely as possible, i. e. until the flow ceased or had reached a constant rate of a few drops per minute. The suboccipital needle was then removed, the head and neck extended, and the contrast medium injected. During the injection, 6 dogs were in the lateral position, and 3 in the prone position.

Number of animals and observation period: Nine. (One of them had been used about 1 hour earlier for an experiment according to A.) One dog was killed 2 days later, owing to deterioration of its general condition (? canine distemper). Three of the remaining dogs were kept under observation for 1 to 2 weeks after the experiment, and 5 for 1 to 3 months.

Duration of elevation of hindquarters: 1.5 min in 1 experiment, 2.5 to 3 min in 7, and 4.5 min in 1 experiment.

C. *Lumbar injection of contrast medium after preceding suboccipital spinal tap, head and neck flexed during injection*

Cervical myelography was performed with the technique described under B, i. e. by lumbar puncture after preceding suboccipital spinal tap, but the flexed position of the head and neck, as well as the position of the suboccipital needle, were retained during and after injection. The dogs were in the lateral position during the injection. In 8 experiments, the spinal fluid flowing from the puncture needle was tested for the presence of contrast medium in high concentration (1 % or over) with the rapid chemical method described earlier. Roentgenologic examination in the lateral position was generally continued until the spinal fluid gave a positive iodine reaction. In 6 experiments, the suboccipital needle was withdrawn after a varying interval, the hindquarters remaining elevated; the head and neck were straightened, after which further roentgenograms were obtained.

Number of animals and observation period: Seven. (Two of them were used for 2 identical experiments at intervals of about 2 weeks.) The observation period after the experiment ranged from 4 days to 4 months, but was from 7 to 14 days in most experiments.

Duration of elevation of hindquarters: 1 to 2 min in 5 experiments, and 4 to 14 min in 4.

D. *Variation in rate of injection*

Myelography was performed according to A and B, respectively, in 3 experiments each, but the contrast medium was injected in the course of about 90 sec, instead of at the standard rate of about 10 sec. The dogs were in the lateral position during injection.

Number of animals and observation period: Six. The observation period after the experiment was 9 days in 1 experiment, and 2 to 3 months in 5.

Duration of elevation of hindquarters: 3 to 4 min.

E. *Penetration of the contrast medium into the intracranial part of the subarachnoid space*

Myelography was performed according to B and C. Methylene blue was added to the contrast medium in such concentration (about 0.5 %) that the tissues with which the solution had been in contact were stained intensely blue. During injection the dogs were in the lateral position. Each group contained 2 dogs; their forequarters were raised for 30 and 60 sec, respectively, after injection. They were killed immediately afterwards by i. v. injection of Mebumal natrium 6 %. With the dog in the same position, the vascular system was perfused with physiologic saline in a dose of about 50 ml/kg bodyweight. Fixation was then performed by intra-arterial

Fig. 1. Myelogram of cervical region of a dog after lumbar subarachnoid injection of Kontrast U 20 % with 1 mg/ml of Xylocaine hydrochloride. Dog in lateral position with hindquarters elevated about 45° and head and neck extended during the injection. Contrast medium arrested in the anterior thoracic and posterior cervical region.

injection of the same quantity of 10 % formalin in physiologic saline. The dog was left with the forequarters raised for 24 hours; it was then decapitated, still in the same position, through the atlanto-occipital joint. After the fluid present in the subarachnoid space had run out, the skull was opened, and the brain removed and inspected.

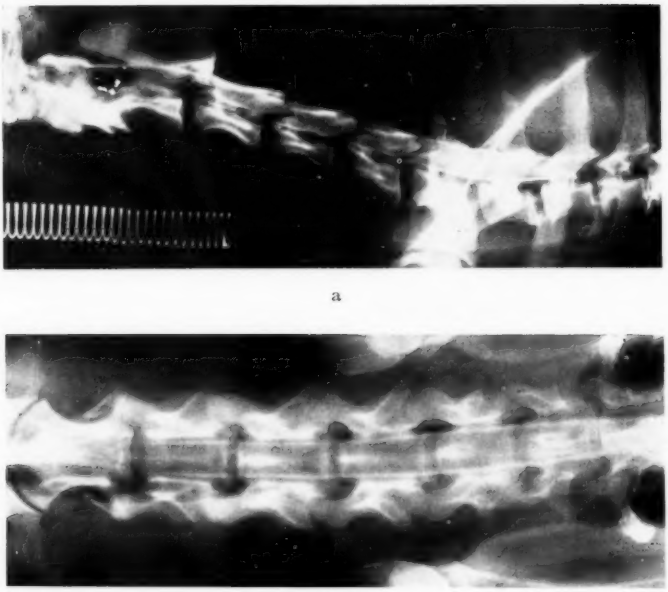
Results I

Passage of contrast medium to the cervical subarachnoid space

In the 3 dogs in which lumbar injection of contrast medium was made with the hindquarters greatly elevated, but without preceding suboccipital spinal tap, the contrast medium was arrested in the anterior thoracic or posterior cervical region (Fig. 1).

In other experiments, the subarachnoid space was emptied of spinal fluid as completely as possible before injection by means of a puncture needle inserted suboccipitally. The contrast medium, in roentgenologically demonstrable concentration, then reached the cranial part of the cervical subarachnoid space very rapidly, often immediately after the end of injection.

The distribution of the medium in the cervical subarachnoid space was greatly influenced by the position of the neck. Thus, when the head and neck of the dog were extended during injection, the ventral part of the space was generally well filled as far as the posterior margin of C2, and the dorsal part to the posterior margin of C1 (Fig. 2). In some dogs, the dorsal line of contrast medium was, however, inconstant over C3 and C4. If, on the other hand, the contrast medium was injected into dogs with the head and neck flexed, it was arrested ventrally behind C4, whereas a marked accumulation of the medium was observed in the ventral part of the subarachnoid space in the transition be-



a

b

Fig. 2. Myelograms of cervical region of a dog in lateral (a) and dorsal (b) positions. Conditions as in fig. 1 except that suboccipital spinal tap, with the neck flexed, was performed immediately before the injection. Subarachnoid space filled ventrally as far as posterior margin of C2 and dorsally to the posterior margin of C1.

tween the cervical and thoracic region (Fig. 3a). In this position, the dorsal line of medium was inconstant. A distinct dorsal line of contrast medium was, however, generally present from the posterior margin of C1 to that of C2 (Fig. 3a). When the head and neck were straightened one or a few minutes after the end of injection, the medium was displaced in the direction of the ventral subarachnoid space (Fig. 3b). Its filling was not, however, as good as when the medium was injected with primary extension of the neck.

In the Table, p 264, is shown the time of appearance of the contrast medium at different points in the cervical subarachnoid space — with sufficient density for diagnostic purposes — in lateral films during myelography according to methods B and C. The numerals 0, 30, 60, 120 in column 2 denote the time at which the exposure was made, counted in seconds from the end of injection. The numerator of the fractions denotes the number of experiments in which contrast medium, at the time in question, was distinctly visible in the subarachnoid space, over the discs specified in the headings of the respective columns.

a

b

Fig. 3. Myelograms of cervical region of a dog. a) Conditions as in fig. 2a, except that the flexed position of the neck for suboccipital puncture was retained during injection, and the puncture needle left in place. Marked accumulation of contrast medium at transition between cervical and thoracic region. Dorsally, a distinct line of medium from posterior margins of C1 to C3. b) Conditions as in (a), and exposure after extending the neck. Medium displaced in the direction of the ventral space.

The denominator gives the total number of dogs examined roentgenologically at the time in question.

Prolongation of the period of elevation of the hindquarters in excess of 60 sec did not result in greater density of the medium, except in 1 dog in group B, in which the medium reached C2/C3 after 2.5 min. In the other experiments the density remained unchanged or decreased successively in exposures made more than 60 sec after the end of injection.

No definite correlation could be demonstrated in the experiments with the neck flexed (group C) between the time of appearance of the iodine reaction in the spinal fluid and the time of optimal density of contrast medium in the cervical subarachnoid space. Thus, in two experiments, the iodine reaction did not appear until after 3.5 and 7.5 min, whereas, from the roentgenologic point of view a satisfactory amount of medium was already present within 1 min after injection.

Comparisons between the quality of the myelograms as regards the ventral

Table

Time of appearance of contrast medium in the subarachnoid space over the anterior intervertebral d[isc]s and the atlanto-occipital joint, respectively.

Position of cervical spine on injection of medium and exposure	Interval between injection and exposure sec	Number of animals with contrast filling over the disc in question in relation to number of animals investigat[ed]						
		C7—C6	C6—C5	C5—C4	C4—C3	C3—C2	C[2]—C1	
Neck extended:								
(B in text)	0	3/4	3/4	2/4	2/4	2/4	[2]/4	
Dorsally	30	3/4	3/4	2/4	3/4	3/4	[3]/4	
	60	5/6	5/6	4/6	3/6	3/6	[3]/6	
	120	3/4	3/4	2/4	2/4	3/4	[2]/4	
	0	4/4	4/4	3/4	2/4	0/4	[0]/4	
Ventrally	30	4/4	4/4	4/4	3/4	3/4	[3]/4	
	60	6/6	6/6	6/6	5/6	5/6	[5]/6	
	120	4/4	4/4	4/4	4/4	2/4	[3]/4	
Neck flexed:								
(C in text)	0	0/6	0/6	1/6	1/6	1/6	[1]/6	
Dorsally	30	1/3	1/3	2/3	1/3	2/3	[1]/3	
	60	2/5	3/5	3/5	2/5	4/5	[2]/5	
	120	0/1	1/1	1/1	1/1	1/1	[0]/1	
	0	5/6	4/6	3/6	0/6	0/6	[0]/6	
Ventrally	30	3/3	3/3	3/3	1/3	1/3	[1]/3	
	60	5/5	5/5	3/5	1/5	1/5	[1]/5	
	120	1/1	1/1	1/1	0/1	1/1	[1]/1	

subarachnoid space on injection with the dog in the prone and the lateral position, respectively, were made only in group B. Of the myelograms of the 3 dogs in which the injection and films were made in the prone position, only one had an amount of contrast medium comparable to that of myelograms with injection in the lateral position.

The duration of injection was prolonged to 90 sec (standard time about 10 sec) in 3 dogs in myelography according to A, and in 3 dogs according to B. The myelograms showed no definite differences as compared to those obtained with a more rapid rate of injection.

After elevation of the forequarters, the contrast medium in the cervical part of the subarachnoid space decreased rapidly in the 6 experiments in group C in which it was checked. In roentgenograms taken about 1 min after elevation, the column of medium was extremely diffuse in this region. In the lumbar region, on the contrary, the medium was relatively dense at this time.

Penetration of contrast medium into the intracranial subarachnoid space

Penetration of the contrast medium into the intracranial part of the subarachnoid space was studied by staining the medium in 2 dogs in group B

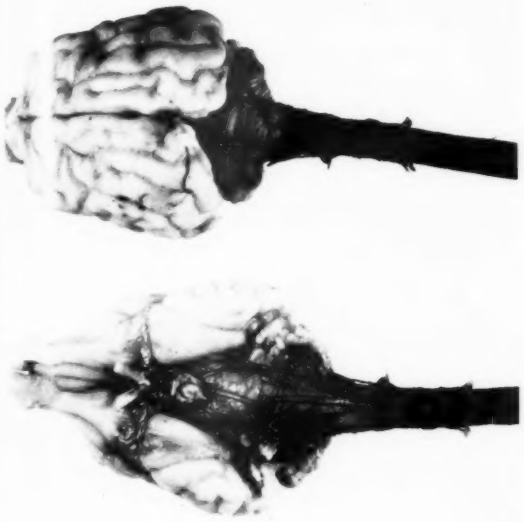


Fig. 4. Dorsal and ventral aspects of brain, medulla oblongata and spinal cord of a dog after lumbar subarachnoid injection of Kontrast U 20 % containing 0.5 % methylene blue, under conditions described in text. Intense blue staining of spinal cord, moderate staining of medulla oblongata, most of surface of cerebellum, and central part of brain stem as far as the optic chiasm.

(injection in the lateral position) and 2 in group C. One dog in each group was placed with the hindquarters elevated for 30 sec after the end of injection, and the other for 60 sec. Inspection of the central nervous system after removal of the dura showed in every case intense blue staining of the spinal cord, and moderate staining of the medulla oblongata and the greater part of the surface of the cerebellum as well as of the ventral part of the brain stem as far as the optic chiasm (Fig. 4). In addition there was faint blue staining ventrally and laterally of the hemisphere that lay lowest in the experiment; the blue colour was particularly distinct along the vessels in the Sylvian fossa. No definite difference was present between the two groups with respect to the extent and intensity of staining.

Neurologic disturbances

1. *Manifestations localized chiefly to the region of innervation of the cranial nerves.* Increased reflex excitability was observed in several experiments on touching the skin of the face during the stage of wakening. In addition, 4 dogs had periodic jaw spasms during this stage as well as increased tonus in the neck muscles with a tendency to a flexor position of the neck to the right. One dog had increased tonus in the extensor muscles of the front legs as well. In 3 of these dogs in which the hindquarters had been elevated for 2, 4.5 and 10 min, respectively, the manifestations lasted 15, 45 and 60 min and ceased without

treatment. In the fourth dog (duration of elevation of hindquarters 2 min 45 sec), generalized epileptiform convulsions appeared 15 min after onset of the other signs. They were arrested by the i. v. injection of pentothal in a dose of about 1 cg/kg bodyweight, and did not recur.

2. *Spinal manifestations.* Of the 25 dogs kept under observation during the first few days after myelography, 4 showed slight to moderate paresis of one hind leg (right leg in 3 cases, left in 1). All 4 dogs had been given further injections of contrast medium, 3 of them as a test injection of 0.5 ml of the medium 10 to 15 min before the main injection, and 1 in the form of two injections (0.5 ml/kg bodyweight) at an interval of about 1 hour. None of the other 21 dogs kept under observation exhibited any motor disturbances attributable to the contrast medium, even though 4 of them had received more than one injection in one of the forms described above.

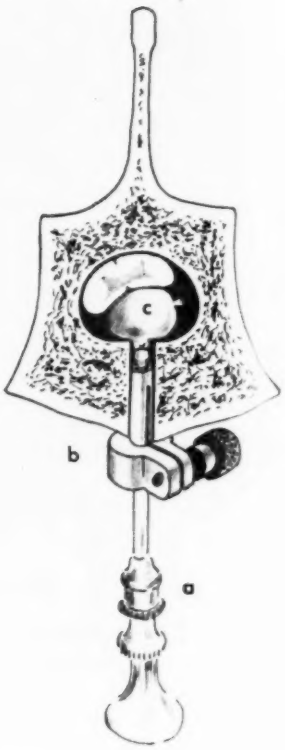


Fig. 5. Apparatus for producing controlled compression of the spinal cord.

Effect on arterial blood pressure

The effect of the injection of contrast medium on the arterial blood pressure was essentially in agreement with the results of earlier investigations (FUNKQUIST & OBEL 1960). The initial rise lay between 100 and 50 mm Hg in 4 experiments, between 50 and 25 mm in 12, and between 0 and 25 mm Hg in 9 experiments. The duration of the rise ranged from 2 to 10 min. No marked difference in the rise in blood pressure elicited by injection of contrast medium was present between the groups.

Systemic disturbances and mortality

One of the 24 dogs (groups A—D) was killed in direct connexion with the experiment. Another dog was killed after a further 2 days because of systemic disturbances (?canine distemper). The remaining 22 dogs survived the experiment, and showed no greater systemic disturbances than those customary after a corresponding duration of anaesthesia alone.

II. Experiments in dogs with experimentally induced spinal cord compression

Compression of the cervical spinal cord was induced in 4 dogs aged 6 months to 1 year and weighing from 7 to 13 kg. This was done by epidural injection of solid paraffin by the following technique.

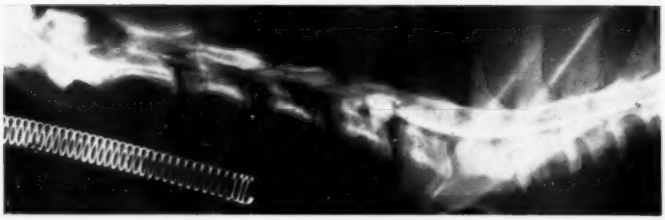
With the dog under pentothal-nitrous oxide anaesthesia, the ventral surface of the cervical spine was exposed. A median hole with a diameter of about 6 mm was bored through the body of one of the cervical vertebrae (C3, C4 or C5) into the vertebral canal. A trocar, approximately 80 mm long (Fig. 5a), with an inner diameter of about 2 mm and an outer diameter of about 3 mm was provided with an outer case (Fig. 5b) fitting the bore hole. To limit a spread of the paraffin in the epidural space, the part of the trocar protruding beyond the outer case was covered by a rubber balloon (Fig. 5c), made by double ligation of a valve rubber. After application of the rubber balloon, the trocar enclosed in its outer case was introduced to such a depth in the bore hole that the outer case was firmly anchored in it. The length of the part of the trocar protruding from the outer case was regulated under fluoroscopic control so that the trocar barely reached the internal orifice of the bore hole.

Four parts by weight of solid paraffin (m. p. 69 to 72° C) and one part of Lipiodol were heated and constantly stirred, over a water-bath to about 100° C and, by means of a warmed glass syringe, 0.1 ml of the mixture was introduced into the trocar. When the mixture had been allowed to cool for about 30 sec, it was pressed into the rubber balloon with the mandrin of the trocar. This procedure was repeated at intervals of about 1 min between filling the trocar, until the dog reacted to introduction of the mandrin by spasms (total quantity 0.1 to 0.8 ml). The trocar was then withdrawn, the rubber balloon being pushed off against the edge of the outer case. Finally, the outer case was also withdrawn from the hole and the muscles and skin were sutured.

Myelography was performed on all 4 dogs 1 to 3 days after the injection of paraffin. It was performed according to technique described under heading I—C, i. e. with the head and neck of the dog flexed during the first few minutes after injection of contrast medium; they were then straightened, and further exposures made 3 to 4 min following the end of injection. The pressure in the femoral artery was recorded by the method of Hansson & Obel (1958). One dog was killed on humanitarian grounds in connexion with myelography. Two dogs were kept under observation for 1 day and 3 days, respectively, after which they were killed. In the remaining case, laminectomy for the purpose of decompression was performed in direct association with myelography. The position and shape of the paraffin plug were studied at autopsy in 3 cases, and at operation in 1 case.

Results II

The effect of paraffin injection ranged from merely a pain reaction on bending the neck to quadriplegia. Optimal filling of the dorsal part of the subarachnoid space as far as the site of compression was obtained as early as within 60 sec. Satisfactory filling of the corresponding ventral region did not occur until the neck and head had been straightened. In 2 cases, traces of contrast medium could also be demonstrated roentgenologically anterior to the site of compression. A positive iodine reaction in the spinal fluid flowing from the suboccipital needle appeared in only one case (2 minutes after the end of injection).



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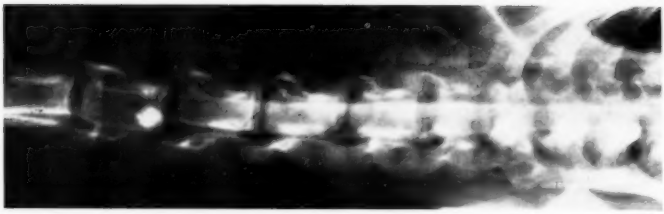

b

Fig. 6. Myelograms of cervical region of a dog with experimentally induced compression of cervical spinal cord. a) Epidural injection of solid paraffin with addition of 20 % lipiodol through C5; dog in lateral position. b) Compression at C3; dog in dorsal position.

The myelographic changes in the form of a filling defect and displacement of the subarachnoid space, respectively, were in good conformity with the position and shape of the compressing paraffin plug (Fig. 6). Of the two dogs kept under observation, one (myelography performed 1 day after injection of paraffin) showed slight aggravation of the signs of compression already present before injection of the contrast medium. No other signs were observed that could be ascribed to an effect of injection of contrast medium on the central nervous system.

The essential changes in blood pressure during and after injection consisted in 3 cases of a rise of 0 to 30 mm Hg with a duration of about 2 min. In the remaining case, the pressure rose about 100 mm Hg for 5 min. In 1 case a brief fall in pressure to 50 mm Hg occurred when the dog was turned onto its back.

III. Experiments in dogs with spontaneous spinal cord compression

The series consisted of 9 dogs (7 dachshunds aged 4.5 to 9 years, and 2 pekineses aged 1 year and 4 years, respectively) with signs of spinal cord compression in the cervical or anterior thoracic region. The clinical features ranged from pain on movement to quadriplegia. All of them underwent cervical

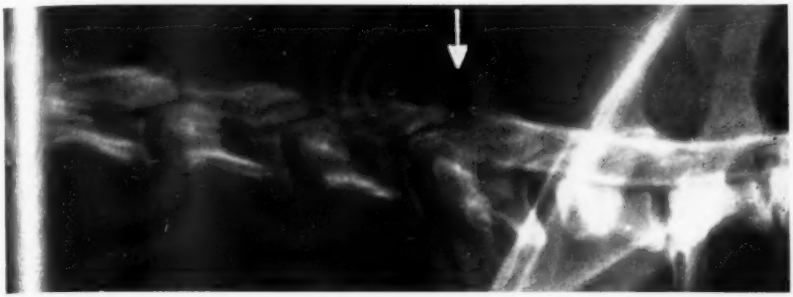

Fig. 7. Myelogram of cervical region of a dog with clinical signs of compression of cervical spinal cord (prolapsed disc); conditions on myelography as in fig. 2a. Filling defect of the cervical subarachnoid space over C5 and 4th intervertebral disc (C5/C6). Dorsal displacement of contrast column over the disc (arrow).

myelography; in 7 cases it was performed according to conditions described under heading I—B (head and neck extended during injection), and in 2 cases according to heading I—C (head and neck flexed during injection and for a certain period following it). All the dogs were in the lateral position during injection.

Myelography was intended to serve as a basis for therapeutic intervention, and in some cases was carried out before the possible risks of the procedure had been investigated. Consequently, the period of elevation of the hindquarters and, as a result, the number of exposures as well, was considerably reduced in certain cases. The pressure in the femoral artery was recorded by the usual method in 8 dogs.

Laminectomy for the purpose of decompression was performed on 3 of the dogs in direct association with myelography. The possible detrimental effect of injection of contrast medium could not therefore be established with certainty, in view of the operative trauma. In 2 cases, the corresponding operation was performed 5 and 7 days, respectively, after the myelographic examination. These 2 dogs and those (4) in which myelography alone was carried out offered a possibility of studying the effects of injection of contrast medium on the existing signs of compression.

Results III

Roentgenologic signs of spinal cord compression could be demonstrated in 8 cases, whereas in 1 case the myelogram was negative. In 7 cases the compression was situated ventrally (over C2—C3 in 1 case, C3—C4 in 1, and C5—C6 in 5 cases) (Fig. 7), and in 1 case ventrolaterally (over Th2) (Fig. 8).

Satisfactory myelograms were obtained in every case, even though the last exposure before elevation of the forequarters was already made a few seconds

Fig. 8. Myelogram of cervical and anterior thoracic region of a dog with clinical signs of compression of thoracic spinal cord (epidural lipoma); conditions on myelography as in fig. 3b. Filling over Th2 (arrow).

after the end of injection in 1 case, and about 60 sec following it in 5 cases. In 2 cases (myelography according to I—B), a sufficient number of films were obtained to judge the time for optimal demonstration of the uncompressed parts of the subarachnoid space (compression at C5—C6). Satisfactory density was present within 30 sec, whereas the myelograms taken after more than 60 sec showed successively decreasing density of the medium.

In the 5 cases in which the epidural space was exposed by laminectomy at subsequent operation, the myelographic findings could be completely verified (cervical prolapsed disc in 4 cases and epidural lipoma in 1).

In a few of the 6 cases in which myelography alone was performed primarily, increased reflex excitability on touching the skin of the face was observed when the dog woke from anaesthesia; this sign regressed in a few hours. At examination 24 hours after recovery from anaesthesia, slight aggravation of the signs of compression motivating the examination was observed in 3 of the 6 dogs mentioned above. The exacerbation subsided within 1 to 2 days in every case. As already pointed out, the effect of injection of contrast medium on the central nervous system could not be judged in the 3 dogs operated on in direct association with myelography, in view of the sequelae of operation; one of them (prolapsed cervical disc) was moribund when operation was performed, and died a few days later. No clinical manifestations that could be ascribed to injection of contrast medium appeared in the other dogs operated upon once they had recovered from the operative trauma.

The arterial blood pressure was largely unchanged in 1 case, moderately raised in 5 cases (rise 30 to 50 mm Hg), and greatly raised in 2 (rise 100 to 120 mm Hg). The rise had a duration of 3 to 7 min. A subsequent, brief fall in blood pressure occurred in 3 cases,the lowest values being 120, 90 and 60 mm Hg. In the first 2 cases, the fall in pressure took place when the dog was turned onto its back or abdomen, respectively, and in the third case in connexion with elevation of the forequarters.

Discussion

T factors seem to be of decisive importance for the passage of contrast med n from the lumbar region into the cervical subarachnoid space. They are:) removal of the spinal fluid from the cervical subarachnoid space before jection of the medium, and (2) the position of the neck during injection.

1. heoretically, the contrast medium in view of its greater specific gravity migh be expected to run down along the lower margin of the subarachnoid space nd reach a sufficient concentration in the cervical region without previous emoval of the spinal fluid. Experiments with technique I—A have, howe r, shown that such an exchange of fluid does not take place, but that the m dium is arrested in the posterior part of the cervical region. This is probably due t the turbulence arising on contact between the contrast medium flowing in an nterior direction and the spinal fluid collected in the cervical and anterior thora ic regions. This dilutes the medium to such a degree that the difference in spe ific gravity necessary for a rapid exchange of fluid no longer exists.

It would obviously simplify matters from the technical point of view if the spinal fluid could be withdrawn through the lumbar needle, with the dog's forequarters elevated and thus avoiding suboccipital puncture, but preliminary experiments showed that removal of the spinal fluid through a lumbar needle was not definitely effective. The probable reason is that the mobile structures present in the lumbar part of the subarachnoid space are apt to block the needle tip when the spinal fluid decreases in volume.

2. When, as can be inferred from the aforegoing, injection of contrast medium must be preceded by suboccipital puncture, it might seem reasonable to leave the suboccipital needle in place during the injection. It would then be possible — using the method for rapid determination of the presence of contrast medium in the fluid flowing from the needle — to elevate the anterior part of the body as soon as the medium had reached the anterior margin of the cervical region. This might diminish the risk of any major quantity of medium passing into the intracranial part of the subarachnoid space. On the other hand, if the suboc ipital needle were to be kept in place during the injection, the head and neck would have to remain in the flexed position used during puncture. No correl tion seems, however, to exist between the time at which a positive iodine reacti n appears in the spinal fluid and the roentgenologically established time at wh ch the contrast medium reaches the anterior part of the subarachnoid space Moreover, the flexed position of the head and neck does not result in satisf ctory filling of this portion of the subarachnoid space. Consequently, in fu re use of the method there seems to be no reason for leaving the suboccip al needle in situ during the injection.

A riori, it did not seem to be ruled out that the position of the anterior part of th spine might also affect the possibility of the medium penetrating into the i racranial part of the subarachnoid space. The results of the experiments

with stained contrast medium do not, however, indicate that the position of the head and neck is of any great importance in this respect.

To sum up, the following statements may be made regarding the role played by the position of the cervical spine during myelography. The extended position gives the best depiction of the anterior part of the cervical subarachnoid space, whereas the flexed position promotes filling of the subarachnoid space in the transition between the cervical and anterior thoracic region. There is no reason to assume from the results of the experiments that any difference exists between the two alternatives from the point of view of safety.

It is remarkable that according to the experiments the risk of any serious damage to the intracranial part of the central nervous system by the contrast medium appeared to be extremely slight. This applied even when the animal lay with its forequarters lowered for a relatively long time after the injection. It is probable that as a result of the animal's position before the injection the intracranial part of the subarachnoid space and the ventricular system were filled with spinal fluid to such a degree that any medium that might have entered was rapidly diluted. Despite this, every endeavour should obviously be made to keep the period of elevation of the hindquarters as short as possible. It is therefore essential to bear in mind that passage of the contrast medium from the lumbar to the cervical region seems to take place very rapidly. On injection with the neck extended, the medium in 5 of 6 experiments reached the level of C2 30 to 60 sec after injection. In the remaining case, the corresponding time was 2.5 min. These results should be considered against the background of the fact that spasms of the facial muscles during wakening from anaesthesia have been observed after elevation of the hindquarters for 2 min after injection of the contrast medium. There therefore appear to be indications, at least in animals of the size used in these experiments, to standardize the duration of elevation of the hindquarters to 60 sec and, when evaluating the myelogram, to take into account that deficient filling of the subarachnoid space above the level of C2—C3 may occur in normal animals.

The only sign of damage to the spinal cord observed in the experimental animals after myelography, was mild or moderate paresis of the muscles of the hind legs with a predilection for the side that was the lower during the injection. This occurred in dogs given more than one injection of contrast medium. The localization of the damage to the lumbar spinal cord is probably dependent on two factors. One is that the concentration of the medium is presumably higher in the lumbar region than in the other parts of the subarachnoid space during and immediately after injection. The other is the longer period for which this region is in contact with the medium (test injection confined to the lumbar region; prolonged exposure of the lumbar region to contrast medium in connexion with elevation of the forequarters). If the aforegoing argument is correct, it may be advisable to reinject spinal fluid through the lumbar needle before elevating the forequarters of the animal.

A udy of the morphologic basis of the functional disturbances will be publ ed separately (FUNKQUIST & OBEL 1961).

Th aggravation of the already existing signs of compression that took place after amination is probably to be ascribed to the contrast medium having prod ed an increase in the volume of the spinal cord. It has, in fact, been show in studies to be reported later that lumbar subarachnoid injection of Kont st U may, under certain conditions, cause oedema of the spinal cord Fun UIST & OBEL 1961).

Th present results seem to suggest the following procedure in cervical myelo raphy with water-soluble contrast media in animals of the size in question. ter lumbar and suboccipital puncture of the subarachnoid space under i. v. a esthesia, anaesthesia and ventilation are maintained by artificial respiration w h nitrous oxide and oxygen, muscle relaxation being produced by administ ation of succinylcholine iodide. The animal is placed in the lateral positio , with the hindquarters well elevated. After suboccipital withdrawal of the inal fluid, Kontrast U 20 % with the addition of 1 mg/ml of Xylocaine hydro loride, is injected in a dose of about 0.3 ml/kg bodyweight. The head and n k of the animal should be kept extended if interest is focused chiefly on exa ination of the ventral subarachnoid space in the middle and anterior parts of the cervical region. If, on the other hand, examination of the subarachnoid space in the anterior thoracic and the posterior cervical region is required, it may be preferable to have the neck flexed. Films of the cervical region are obtained during about 60 sec, counted from the end of the injection, after which the forequarters are elevated so that the contrast medium falls to the thoracic and lumbar regions.

SUMMARY

Cervical myelography with a water-soluble contrast medium was performed in healthy dogs, in dogs with experimentally induced compression of the cervical spine, and in dogs with spontaneous spinal cord compression. Filling of the cervical subarachnoid space was obtained by the lumbar injection of a mixture of contrast medium and Xylocaine with the hindquarters of the animal elevated, following the suboccipital withdrawal of spinal fluid. The method did not appear to be associated with any risk of serious circulatory disturbances or persistent damage to the central nervous system.

ZUSAMMENFASSUNG

Cervi le Myelographie mit einem wasserlöslichen Kontrastmittel wurde bei gesunden Hunden mit sperimentell hervorgerufener Kompression des Cervicalmarks und bei Hunden mit spontan Rückenmarkkompression durchgeführt. Ausfüllung des cervicalen Subarachnoidalraumes urde durch lumbale Injektion einer Mischung von Kontrastmittel und Xylocain bei erhöhter Hinterteil des Tieres erreicht, wenn die Rückenmarksflüssigkeit durch suboccipitale Punktio vorher entfernt vurde. Die Methode scheint mit keinem Risiko für ernste Zirkular sstörungen oder Schädigung des Zentralnervensystems verbunden zu sein.

RÉSUMÉ

L'auteur a fait des myélographies cervicales avec un moyen de contraste hydro-solu[ble] sur des chiens sains, des chiens présentant une compression expérimentalement provoqué[e] de la moelle cervicale et des chiens ayant une compression médullaire spontanée. Après so[us]-traction de liquide céphalo-rachidien par ponction atlo-occipitale, l'opacification de l['espace] sous-arachnoïdien cervical est obtenue par l'injection d'un mélange de moyen de con[traste] et de Xylocaïne par voie lombaire en surélévant l'arrière-train de l'animal. Cette m[éthode] semble n'entraîner ni danger, ni perturbation circulatoire grave, ni lésion du [système] nerveux central.

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FROM RADIUMHEMMET (DIRECTOR: PROF. SVEN HULTBERG), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN.

INCIDENCE OF HYPOTHYROIDISM AND RECURRENCES FOLLOWING I^{131} TREATMENT OF HYPERTHYROIDISM

by

ULLA BELING and JERZY EINHORN

Several large series of hyperthyroid patients treated with I^{131} have been reported (CHAPMAN & MALOOF 1955, CLARK & RULE 1955, LARSSON 1955, BEIERWALTES & JOHNSON 1956, MCCULLAGH 1956, WERNER et coll. 1957, DEGOVIN et coll. 1959, LEVINSON 1959, BLOMFIELD et coll. 1959, SHELINE & MILLER 1959, ELLER et coll. 1960). In the present material the patients were subjected to regular follow-up examinations, usually at the laboratory where they had received the I^{131} treatment. The aim of this investigation was to study long-term complications, notably the incidence of hypothyroidism — as well as recurrences of hyperthyroidism — at varying intervals after treatment. Part of the series, the patients treated between 1951 and 1953, has previously been reported (LARSSON).

Material. The series consists of patients referred to Radiumhemmet for I^{131} treatment of hyperthyroidism. More than half of them had been referred from the goiter clinic at the Surgical Department of St. Görans Sjukhus (Dr Hjalmar Viljnbladh). During the period from 1951 through 1956 a total of 854 patients received radioiodine therapy at Radiumhemmet for hyperthyroidism. The present series is limited to patients followed up for at least two years, and does not include 58 who died within two years after the last I^{131} treatment.

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Table 1

Follow-up time in the total series

Years after I^{131} therapy	2—3	3—4	4—5	5—6	6—	>7
Number of patients followed up	791	672	451	284	16	51

Of the remaining 796 patients, 791 or 99.4 per cent had been followed up for 2 to 8 years. Five patients were not available for control.

Of the above-mentioned 791 patients, 654 were females and 137 males. The ages ranged from 19 to 82 and averaged 54.6 years. Patients under the age of 40 were treated with I^{131} only on special indications; the series includes 105 such patients. The age distribution is shown in Table 3.

Methods

The principles of treatment have been previously reported (LARSSON). The method for determination of the initial I^{131} dose was based on estimation of the thyroid weight, the 24-hour radioiodine uptake, and the effective half-life of I^{131} in the thyroid, the aim being to deliver 6 000 to 10 000 rep to the gland. In young patients the calculated initial radiation dose was often less than 6 000 rep, and in old patients with nodular goiter, sometimes greater than 10 000 rep. For estimating the weight of the thyroid we usually relied on palpation. We sought in some cases to estimate the size of the gland by outlining of the frontal silhouette (HIMANKA & LARSSON 1955) with a heavily collimated directional counter or, at a later period, by examination with an automatic scintigraph. In some patients the effective half-life of I^{131} in the thyroid was not estimated and the dose was determined largely with respect to the size of the gland. Retreatment doses, when indicated, were calculated with respect to the effect of the preceding dose. Only in a few cases was the radioiodine combined with other specific agents.

Radioiodine treatment was repeated at intervals of 2 to 4 months, provided the patient remained toxic and the thyroidal I^{131} uptake remained elevated; otherwise follow-up examinations were made every 2 to 4 months during the first year and subsequently at longer intervals, usually 6 months to 1 year. Patients were usually examined at Radiumhemmet as well as by the surgeon or physician who had originally referred them for I^{131} treatment. In addition to the clinical examination, radioiodine tracer tests were repeatedly made. Where classification was doubtful, the B. M. R., serum cholesterol and P. B. I. were used as criteria.

Classed as hypothyroid were all patients requiring permanent thyroid replacement therapy. During the first few months after I^{131} treatment, transient hypothyroidism may occur. The general policy in this series was to avoid thyroid substitution for the first 4 to 5 months after treatment. In a few cases, however, thyroid substitution was for special reasons instituted earlier in order to prevent the development of severe hypothyroidism. Where thyroid replacement therapy was instituted one year or more after the radioiodine treatment, the clinical picture and laboratory tests had shown unquestionable hypothyroidism. No systematic attempts were made to withdraw replacement therapy once it had been initiated (cf. WERNER et coll.). Some patients discontinued the treatment either of their own accord or, in view of the clinical picture, on our advice. The result in most cases was a return of the clinical hypothyroidism (cf. WERNER et coll., DEGOVIN et coll., RUBENFELD et coll. 1959). Those occasional cases in which it was subsequently possible to withdraw replacement therapy were not classed as hypothyroid.

For patients who had received several I^{131} treatments the follow-up time is counted from the last treatment (See Table 1).

A gnosis of recurrent hyperthyroidism following I^{131} treatment was recorded when recurrence had been detected one year or more after the last treatment.

Statistical methods. The cumulative incidence of hypothyroidism m years after the I^{131} treatment was calculated thus:

$$r = 1 - q_1 \cdot q_2 \cdot q_3 \cdot \ldots \cdot qm \tag{1}$$

where $1 - q_1$ is the incidence of hypothyroidism during the first year after I^{131} treatment; $1 - q_2$ is the incidence of hypothyroidism during the second year after I^{131} treatment, etc.

$$1 - q_i = \frac{a_i}{n_i - \frac{d_i}{2}} \tag{2}$$

where a_i = the number of patients who became hypothyroid during year i; n_i = the number of followed-up euthyroid patients at the beginning of year i; d_i = the number of euthyroid patients followed up for $i - 1$ years but not for i years.

$$n_{i+1} = n_i - a_i - d_i \text{ and hence} \tag{3}$$

$$q_i = \frac{n_{i+1} + \frac{d_i}{2}}{n_i - \frac{d_i}{2}} \tag{4}$$

Since the patients were treated at different periods and some deaths occurred during the follow-up period, the number fell as the duration of observation increased. The results are often reported in the form of curves showing the cumulative incidence of hypothyroidism in relation to the time elapsed since the last I^{131} treatment. Each point on a curve signifies the incidence of hypothyroidism for at least 50 patients controlled.

Results

The incidence of hypothyroidism at follow-ups at varying intervals after the I^{131} treatment is shown in Fig. 1a. One year after the conclusion of radioiodine therapy, 7.46 per cent of the patients were hypothyroid. During the subsequent observation period approximately 3 per cent of the patients developed hypothyroidism each year. This tendency continued throughout the follow-up period. Seven years after I^{131} treatment the cumulative incidence of hypothyroidism amounted to 26.5 per cent.

With the aim of studying the influence of various factors on the incidence of hypothyroidism the patients were grouped with respect to sex, type of goiter, age at the time of I^{131} treatment, and number of I^{131} therapy doses administered.

Factors influencing the incidence of hypothyroidism

The *sex* distribution of hypothyroidism, as shown in Fig. 1b, was even.

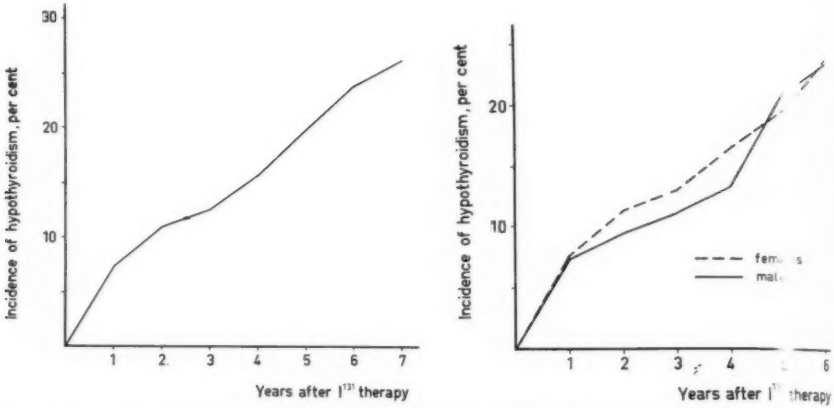

Fig. 1. Incidence of hypothyroidism after I^{131} treatment of 791 patients controlled for 2 to 8 years. Each incidence is based on the number of patients followed up (Cf. Table 1). a) Incidence at varying intervals. b) Incidence distribution according to sex (654 females and 137 males).

Type of goiter. The series was grouped as follows:

	Number of patients
Hyperthyroidism without demonstrable goiter (including 78 patients with recurrent hyperthyroidism following thyroidectomy)	298
Diffuse toxic goiter	218
Toxic nodular goiter	
Small or moderate goiter	167
Large nodular goiter	108

The clinical distinction between diffuse and nodular goiter is an arbitrary one (cf. MORTENSEN et coll. 1955). In this series the diagnosis of nodular goiter was made if one or more discrete nodules were definitely palpable within the gland.

As previously reported, the hyperthyroid patients without demonstrable goiter had, after I^{131} treatment, a higher incidence of hypothyroidism than those with palpable thyroid enlargement. In our series the respective incidences one year after the treatment were 11.4 and 5.1 per cent. Furthermore, the incidence of late hypothyroidism was also greater in patients without demonstrable goiter. From the second to the fifth year after I^{131} therapy an additional 15.3 per cent of patients without demonstrable goiter became hypothyroid, compared with only 10.7 per cent of those with palpable thyroid enlargement. Patients with diffuse and those with nodular goiter differed only slightly in the incidence of hypothyroidism. The difference was likewise small when only the patients with very large nodular goiter and those with diffuse goiter were compared (Fig. 2a).

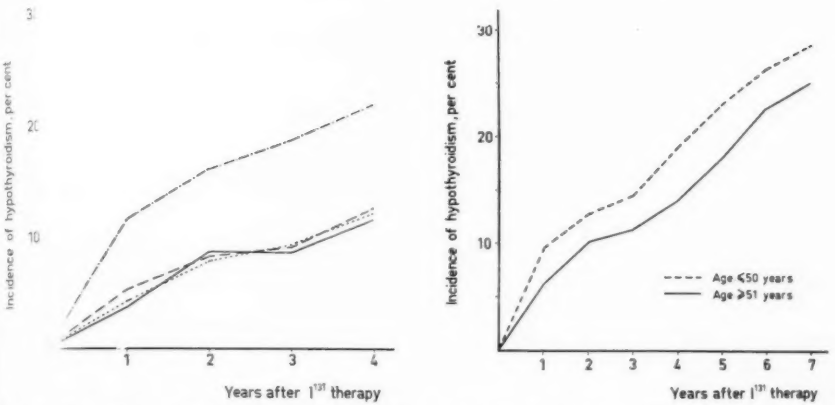

Fig. 2. a) Incidence of hypothyroidism following I^{131} therapy in 298 hyperthyroid patients without demonstrable goiter (— · — · — ·), 218 with toxic diffuse goiter (— — —), 167 with small or moderate toxic nodular goiter (.....), and 108 with large toxic nodular goiter (————).
b) Incidence of hypothyroidism in different age groups.

Seed & Jaffe (1953), Clark & Rule, Larsson, Beierwaltes & Johnson and Levinson found in their series a substantially lower incidence of hypothyroidism after I^{131} treatment of toxic nodular goiter than after treatment of 'exophthalmic' (both diffuse enlarged and non-palpable) goiter. Similar observations have been made after surgical treatment of hyperthyroidism (Crile & McCullach 1951, Bartels 1953, Efskind & Cappelen 1955, Fowler et coll. 1956, Beahrs et coll. 1956). In our series, too, a higher incidence of hypothyroidism after I^{131} treatment was observed in patients with 'exophthalmic' goiter. It was the group of hyperthyroid patients without demonstrable goiter, however, which were responsible for this. The patients with diffuse enlarged toxic goiter in our series showed, after long follow-up times, approximately the same incidence of hypothyroidism as those with nodular goiter. In the nodular goiter cases the incidence of hypothyroidism was, however, somewhat lower one year after the I^{131} treatment (Fig. 2a). Werner et coll. likewise found a relatively high incidence of late hypothyroidism following I^{131} treatment of nodular goiter. In their series of 525 patients, 40 were hypothyroid within one year after the treatment. Only two of those 40, but 7 of the 38 whose hypothyroidism was of later onset, had initially had toxic nodular goiter. Several of our patients who became hypothyroid had, following the I^{131} treatment, substantial residue of the nodular goiters. Similar observations have been made after surgical treatment of hyperthyroidism (Efskind & Cappelen).

Table 2

Initial I^{131} dose (mC) in different groups of patients. In none of the 37 patients with large nodul goiter who were cured by one dose of I^{131} was hypothyroidism observed during the follow-up peri

	Number of patients	Initial I^{131} dose in the total series		Patients euthyroid after one I^{131} dose		Patients hy thy-roid after I^{131} do se	
		Mean	Range	Mean	Range	Mean	Sm llest do pro-d ing hy thy-ro lism
Hyperthyroidism without demonstrable goiter.....	298	4.1	1 — 10	4.3	1.5— 8	4.5	2
Toxic diffuse goiter .	218	6.2	1.5— 30	6.2	2— 30	6.4	3
Toxic nodular goiter, small or moderate.	167	7.9	1.5— 30	8.4	2— 30	8.7	3
Large toxic nodular goiter	108	30.8	6 —105	39.0	15—105	—	–

Of the groups investigated, the highest incidence of hypothyroidism was found in the patients with postsurgical recurrence of hyperthyroidism and no demonstrable goiter, the incidence being 16.7 per cent one year after I^{131} treatment and 31.6 per cent five years after the treatment.

The incidence of hypothyroidism in each group of patients must depend, at least to some degree, on the dosage of I^{131} administered (See Table 2). However, in other series too, the proportion of patients developing hypothyroidism falls with increasing gland mass (LARSSON, and BLOMFIELD et coll.; cf. CASSIDY & ASTWOOD 1959) and is highest following I^{131} treatment of postsurgical recurrence (CLARK & RULE, LARSSON). This finding has been attributed to overestimation of the size of non-palpable goiters and hence overdosage of I^{131} (LARSSON, BLOMFIELD et coll.), and in some at least of the cases that explanation is doubtless correct. It is noteworthy, however, that even the incidence of late hypothyroidism has been greater in patients without demonstrable goiter. This finding too, is possibly attributable to an I^{131} overdosage which for a time has been compensated. It is quite likely, however, that radioiodine treatment of small thyroid glands will result in a higher incidence of hypothyroidism even after ideal dosage of I^{131}.

Age. The incidence of hypothyroidism, as previously reported (Larsson 1955), was higher in the younger than in the older subjects. In our series 9.6 per cent of the patients aged under 50, and 6.3 per cent of those past 50, developed hypothyroidism within one year. The incidence of late hypothyroidism was the same in young and old patients (Fig. 2b). The differences

Table 3

Age distribution with respect to incidence of hypothyroidism one year and five years after radioiodine treatment. Only 23 patients over 70 had been followed up for 5 years.

Age	Number of patients	Hypothyroid % One year after I^{131} therapy	Hypothyroid % Five years after I^{131} therapy
⩽40	105	11.4	24.0
41—50	175	8.6	22.8
51—60	218	7.8	20.0
61—70	213	5.2	13.4
>70	80	5.0	—

that arose in the incidence of hypothyroidism in connection with the treatment remained unchanged at the control examinations. Seven years after I^{131} therapy the cumulative incidence of hypothyroidism was 28.8 per cent in patients aged under 50 and 25.3 per cent in those aged over 50. On division into subgroups, the age dependence of this incidence was even more conspicuous (Table 3).

The types of goiter in different age groups are shown in Table 4. In older patients hyperthyroidism without palpable goiter was more common than in younger patients. In the older patients nodular goiter was found more frequently than diffuse goiter, though this cannot account for their lower incidence of hypothyroidism after I^{131} therapy (see Fig. 2a).

The older subjects were often treated with somewhat higher doses in order to bring about a relatively swift remission. The tendency, moreover, was to give smaller I^{131} doses in younger patients in order as far as possible to obviate hypothyroidism. This condition was nevertheless more common in the younger subjects. The thyroid glands of young patients appear to be more susceptible to I^{131} treatment, and thus lower radiation doses should be given.

Number of I^{131} treatments per patient. The hyperthyroidism was controlled by a single dose of I^{131} in 48 per cent of the patients, while 32 per cent required two doses. A total of 69 (8.7 per cent) received four or more doses. On the average, 1.79 therapy doses of I^{131} were administered per patient.

The patients cured by one I^{131} dose showed the highest incidence of hypothyroidism (Fig. 3a). Worthy of note is the low incidence of early and late hypothyroidism in patients who had received four or more therapy doses

Table 4

Age distribution of goiter types

Age	Hyperthyroidism without demonstrable goiter %	Toxic diffuse goiter %	Toxic nodular goiter %
⩽50	34.6	42.9	22.5
>51	39.1	19.6	41.3

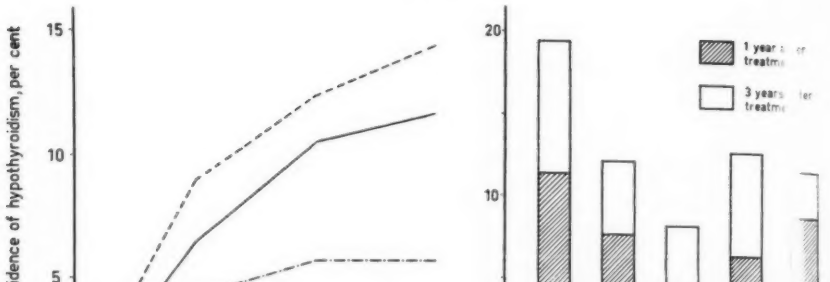

Fig. 3. a) Incidence of hypothyroidism in relation to number of I^{131} doses administered. b) Incidence of hypothyroidism in relation to year of I^{131} treatment. Roman numerals indicate: I — year of treatment, II — Number of patients, III — Mean age, IV — Average number of I^{131} doses administered.

of I^{131}. These patients were few in number, i. e. 69, though 56 of them were controlled for at least three years.

The incidence of hypothyroidism in these different groups depends to some extent on the size of the initial I^{131} dose and the magnitude of the re-treatment dosage. In other major series too (SEED & JAFFE, SHELINE & MILLER, LEVINSON) hypothyroidism has been more common after a single dose than after multiple doses. BALLS et coll. (1955) found the reverse in their series.

Those of our patients who had received several I^{131} therapy doses showed a lower incidence of hypothyroidism. The explanation may be that subjects who are more resistant to radiation treatment and require several doses are less likely than the others to develop hypothyroidism; or it may be that fractionation of the treatment is in some way responsible for the better results.

Incidence of hypothyroidism in patients treated during different periods

The incidences of hypothyroidism in patients treated during different periods were compared in order to ascertain the degree to which the results improved with mounting experience. This series comprises patients treated during the period 1951—1956. In 1951 and 1952 the patients were relatively few and were therefore combined in a single group consisting of 115 subjects; otherwise the patients were grouped according to the calendar year of I^{131} therapy. Since the calendar year was determined arbitrarily by the date of

the last treatment, some measure of selection occurred: the patients who required several I^{131} doses were under-represented in the groups treated during the first years; otherwise the groups treated at different periods were comparable in respect to age and goiter types. Of particular interest are the years 1951 through 1954, when all doses were determined by one examiner whose experience of I^{131} therapy increased year by year.

Between the years 1951 and 1954 the incidence of hypothyroidism one year after radioiodine treatment fell gradually from 11.3 to 4.0 per cent; subsequently it rose again, probably because other less experienced therapists had begun to take part in treatment of the patients (Fig. 3b). The declining incidence between 1951 and 1954 was accompanied by some rise in the average number of treatments required. This rise was partly attributable to the fact that patients requiring several doses were under-represented, notably in the groups treated during 1951 and 1952. In an earlier survey of the series from 1951–1953 (LARSSON) the year of I^{131} therapy was based on the date of the initial treatment. The patients registered for I^{131} therapy in 1951 and 1952 had required, on the average, about the same number of treatments as those treated in 1953, and the decrease in the incidence of hypothyroidism within one year after treatment was comparable with that reported here.

The results of treatment may be expected to improve with the therapist's increasing experience. A reduction of hypothyroidism to almost one-third of its original incidence is — although coinciding with a certain rise in the duration of treatment — a remarkable improvement which illustrates the importance of experience in dealing with the numerous uncertain factors encountered in I^{131} treatment of hyperthyroidism.

Incidence of recurrence of hyperthyroidism after I^{131} treatment

Some patients exhibit, after I^{131} treatment, a temporary drop in their indices of thyroid function, followed within a few months by a return to a level consistent with a clinically lesser degree of hyperthyroidism than that present before the treatment (GORDON et coll. 1950, LARSSON; CHAPMAN & MALOOF; ODDIE et coll. 1959). Such cases were not classed as recurrences of hyperthyroidism. Recurrence of hyperthyroidism one year or more after the last I^{131} treatment was observed in three of our patients (0.38 per cent), two with nodular and one with diffuse goiter. Remission was readily induced by retreatment with I^{131}. Recurrences are seldom found after remissions of one year or more following I^{131} therapy: the reported incidence in major series varies between zero and 1.1 per cent (Table 5).

None of the patients treated with I^{131} at Radiumhemmet for hyperthyroidism died from, or acquired, leukemia or thyroid carcinoma. The follow-up time is too short, however, for evaluation of the frequency of those complications following radioiodine therapy.

Table 5

Incidence of recurrent hyperthyroidism following I^{131} treatment

Source of data	Number of patients treated	Recurrence of hyperthyroidism number of cases
Chapman & Maloof 1955	520	1
Clark & Rule 1955	628	3
McCullagh 1956	1 235	2 (8)
Werner et coll. 1957	525	6
Cassidy & Astwood 1959	200	0
Eller et coll. 1960	1 308	12
Present series	791	3

Discussion

Hypothyroidism occurring several years after I^{131} treatment has often been reported (Seed & Jaffe; Beierwaltes 1953; Larsson; Chapman & Maloof; Werner; Blomfield et coll.; Sheline & Miller, and others).

Werner et coll. in their material of 525 patients, found that 7.6 per cent became hypothyroid during the first year after treatment and an additional 7.2 per cent exhibited myxedema more than one year after treatment. The incidence of hypothyroidism more than one year after the treatment was calculated, however, in relation to the total series and not in relation to the number of patients followed-up.

Cassidy & Astwood found that of 200 patients with follow-up times of 1—7 years, 8 per cent were hypothyroid within one year after I^{131} therapy. The incidence of hypothyroidism rose during the ensuing years and, five years after treatment, was reported to be 14.5 per cent. It had been calculated, however, not in relation to the number of patients examined at each control but in relation to the total series. When the first 101 patients treated in that series were reported (Andersson 1954), 5.8 per cent of those controlled for at least six months were hypothyroid. On re-evaluation after a longer observation time (Cassidy & Astwood), the incidence of hypothyroidism had risen to 26 per cent.

MacGregor (1960) found in his series a 12 per cent incidence of hypothyroidism one year after, and a 17 per cent incidence three years after I^{131} therapy.

In the present series 7.46 per cent of the patients developed hypothyroidism within one year after the radioiodine treatment, a figure closely according with the results calculated for other large series. The cumulative figure for hypothyroidism seven years after the treatment was 26.5 per cent. The curve showed no tendency to level off during the observation period (Fig. 1a), and to judge by its course the incidence of hypothyroidism will rise further as the observation time increases.

H ›othyroidism is not regarded as a serious complication, for as a rule it can ‹ readily controlled by substitution therapy. When occurring one year or ı ‹re after the radioiodine therapy, however, it has a gradual, insidious onsc and there is a danger that many patients will fail to perceive that something is wrong. Frequently there is prolonged, mild hypothyroidism which grac ılly, sometimes over the course of several years (CHAPMAN & MALOOF), deve ‹ps into complete myxedema. ASTWOOD (1960) writes: "The insidious prog ‹ssion of the myxedema overtakes them so gradually that they lapse into this ‹ orbid state without recognizing what is wrong." THORÉN & WIJNBLADH (195 in a follow-up investigation of surgically treated patients, found that: "It i not until the follow-up that some cases of hypothyreosis were diagnosed. The‹ patients had on the whole been satisfied and had considered themselves in g‹ d health." In view of the high incidence of hypothyroidism after I^{131} ther‹ y, patients treated by that method should be followed up indefinitely. Whe‹ this is impracticable, the patient should be informed about this evide tly common complication.

If ‹ifferent series of hyperthyroid patients are to be compared in regard to thera‹ eutic results, the observation time will have to be taken into account when calculating the incidence of hypothyroidism. This incidence will rise with more careful examination and with longer follow-up times.

Patients may even develop hypothyroidism several years after the surgical treatment of hyperthyroidism. A comparison with surgical series with long follow-up times (HURXTHAL et coll. 1945, BARTELS; THORÉN & WIJNBLADH; BORGSTRÖM 1956; IVERSEN et coll. 1957) suggests that hypothyroidism is far more common after I^{131} therapy than after surgical treatment. Atrophic lesions of cells, blood vessels, and stroma that have been observed in the thyroid gland several years after radioiodine treatment (LINDSAY et coll. 1954, CURRAN et coll. 1958) probably account for the high incidence of late hypothyroidism following I^{131} therapy. No corresponding pathologic changes have been noted after the surgical treatment of hyperthyroidism (CURRAN et coll.). The atrophic lesions are probably manifestations of radiation damage, though they could possibly be the result of auto-immunization consequent upon the release of thyroglobulin into the blood stream in connection with the treatment. This hypothesis might be either confirmed or disproved by immunologic studies of patients treated with radioiodine and thereafter followed up over long periods.

The question is bound to arise whether the incidence of late hypothyroidism could not be reduced by modification of the therapeutic technique. In treatment with a single I^{131} dose, 75 per cent of the radiation dose will be delivered to the thyroid within the course of ten days if the effective half-life of radioiodine in the gland is, for example, five days. It is conceivable that with more protracted irradiation the more radioresistant parts of the gland would be better preserved and subsequent atrophy would be reduced. MYANT (1953)

has discussed such a technique involving small I^{131} doses repeated at int[e]rvals of 1 to 2 weeks. If the high incidence of late hypothyroidism is due to [a]uto-immunologic reactions, perhaps administration of corticosteroids in con[j]unction with the radioiodine therapy might reduce the frequency of hypothy[r]oidism.

Recurrence of hyperthyroidism following I^{131} therapy is rare: the inci[d]ence in the present series was 0.38 per cent. Hyperthyroidism recurs more [c]ommonly following surgical treatment, especially of the less radical kind (H[E]RXTHAL et coll.; CRILE & MCCULLAGH). Recurrences may be found [m]any years after subtotal thyroidectomy (CRILE & MCCULLAGH; BARTELS; CHA[P]MAN & MALOOF; THORÉN & WIJNBLADH), just as hypothyroidism may de[v]elop many years after I^{131} therapy.

Acknowledgements

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SUMMARY

The incidences of recurrence and of hypothyroidism were studied in 791 patients at varying intervals after I^{131} treatment of hyperthyroidism. Radiotherapy with I^{131} tends to lead to hypothyroidism, both early and, especially, late. After a long remission, however, there is small likelihood of recurrence of hyperthyroidism. The influence of sex, age, type of goiter and number of I^{131} therapy doses administered on the incidence of hypothyroidism was studied.

ZUSAMMENFASSUNG

Das Auftreten von Rezidiven und Hypothyreoidismus wurde bei 791 Patienten in verschiedenen Intervallen nach Behandlung von Hyperthyreoidismus mit J^{131} studiert. Die Strahlenbehandlung mit J^{131} scheint oft zum Hypothyreoidismus zu führen, sowohl kurze Zeit als auch besonders lange Zeit nach der Bestrahlung. Nach einer langen Remission ist jedoch die Wahrscheinlichkeit für das Auftreten eines Rezidives des Hyperthyreoidismus gering. Der Einfluss des Geschlechts, des Alters, des Strumatypus sowie der Anzahl der J^{131}-therapiedosen auf das Auftreten des Hypothyreoidismus ist studiert worden.

RÉSUMÉ

La fréquence des récidives et de l'hypothyroïdie a été étudiée sur 791 malades à différents intervalles après traitement de l'hyperthyroïdie par l'I^{131}. Le traitement par l'I^{131} a tendance à entraîner une hypothyroïdie, précoce, et surtout tardive. Mais, après une longue rémission, la récidive de l'hyperthyroïdie est peu probable. Les auteurs ont étudié l'influence du sexe, de l'âge, du type du goître et du nombre de doses d'I^{131} sur la fréquence de l'hypothyroïdie.

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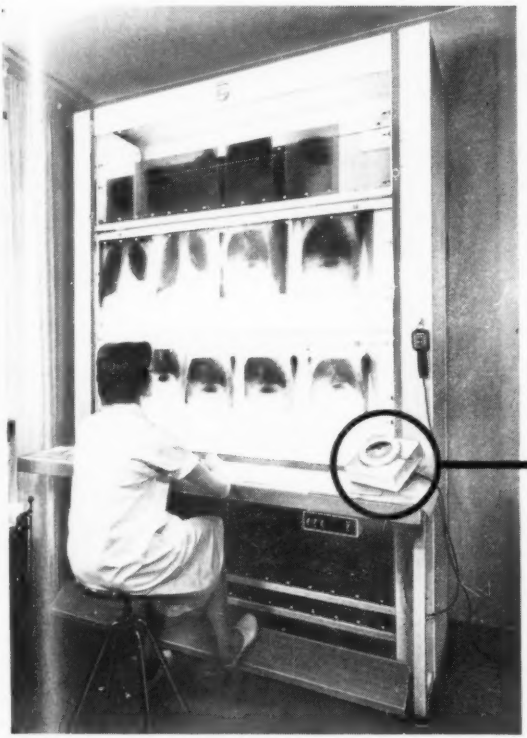

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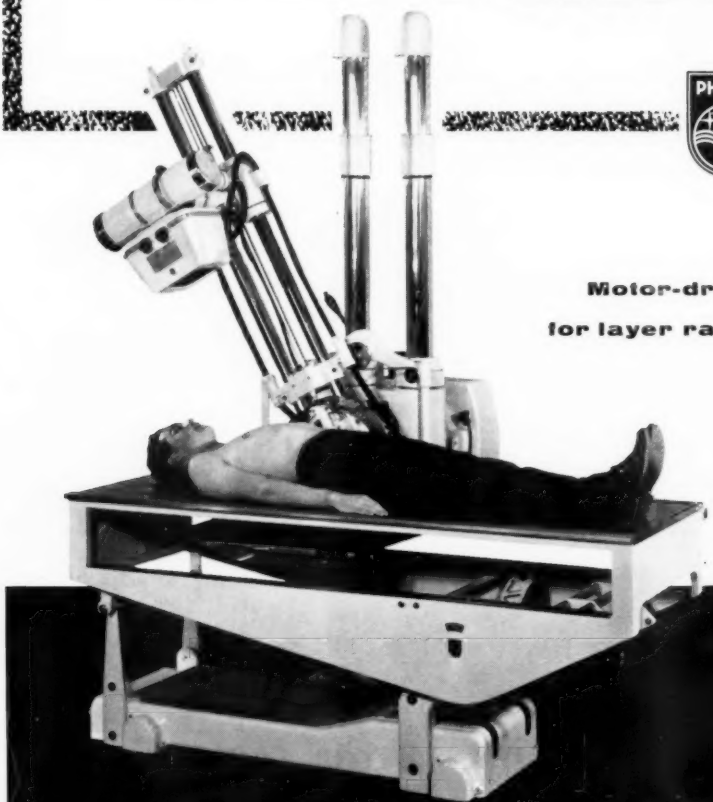

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RECTAL DOSE AND RECTAL DAMAGE IN THE INTRA-CAVITARY TREATMENT OF UTERINE CANCER

by

PAUL STRICKLAND and C. GREGORY

It is common clinical experience that the reaction of normal tissues to irradiation is very variable. In the most standardised techniques, reactions may vary from mild to severe within a single group of cases, and even if dose discrepancy between that recorded and that actually given is in the region of 10 per cent this is quite insufficient to account for the gross differences observed.

We thought it would be interesting to measure and record as accurately as possible the gamma ray dose given to the anterior rectal wall during the course of routine radium, or radio-active cobalt treatment of cancer of the uterus. We hoped to find out from these observations if there was any correlation between the incidence of rectal reactions and the measured rectal dose.

For treatment of carcinoma of the cervix a modified Stockholm technique is used. This consists of one 50 mg intra-uterine tube and two 30 mg ovoids, with modifications of loading if necessary. Carcinoma of the body of the uterus is treated by means of an arrangement of Co^{60} sources, the method of treatment having been described elsewhere (JONES 1952, STRICKLAND 1953). All cases were treated routinely and no modification was made of treatment time or technique as a result of rectal dose rate measurements.

Submitted for publication 17 February 1961.

Apparatus. A scintillation probe and amplifier unit was used for the measurement of rectal dose rate, the basic circuit for the unit having been originally described by GRIFFITH and SWINDELL (1951). In our version of the instrument the scintillation probe consisted of a sodium iodide crystal (thallium activated), a perspex rod and photomultiplier. The crystal and perspex rod were contained in a brass tube of an outside diameter of 0.4 cm and length 1 cm, making a light-tight attachment to the photomultiplier tube. Suitable graduations were marked along the length of the tube. The unit has variable E. H. T., and gain controls making it suitable for a range of dose rate levels, the light output from the crystal appearing on a 0 to 5 μ ampèremeter after amplification. In order to provide for constancy of performance over a long period, a radium jig was constructed to fit closely round the end of the probe. With the jig in position the amplifier gain could be adjusted to give a predetermined reading, thus allowing for variation in sensitivity of the amplifier and photomultiplier units.

Calibration. A detailed calibration of the instrument and check on performance were necessary before the clinical measurements were started, and subsequent checks on the instrument sensitivity and on the calibration curve were made during its period of use. The crystal has directional properties and quality dependence and the importance of these disadvantages were assessed so that appropriate corrections could be made to the clinical measurements.

The directional properties of the crystal and light guide were investigated using a discrete source of radium placed at various angles to the probe-axis and at varying distances from the crystal. Improvements were made to the crystal mounting as a result of these measurements and finally the sensitivity was found to be uniform to within 5 per cent, the response of the crystal being greater for the source placed on the probe axis. For extended sources distributed around the probe, in a way such as would be encountered clinically, the variations in sensitivity would not be as large as 5 per cent.

The response of the crystal probe to radiations of widely different qualities indicated that the crystal response to radiations of mean energy 80 kV was approximately thirty times the sensitivity found for the gamma rays from radium and Co^{60}. The most satisfactory method of obtaining a calibration factor for the probe was to make measurements in a phantom material with an ionization chamber and make a direct comparison of these with measurements made using the probe. A water phantom was considered the most convenient, and gynaecological sources consisting of ovoids and tubes were placed in the phantom in a configuration which simulated the ideal treatment conditions. The ionization chamber or probe was placed in a fixed position relative to the distributed sources and water added to the phantom to various levels. It was found in this experimental set-up that the maximum dose rate

reading occurred when the scintillation probe was covered by 4 cm of water and that this maximum reading was 35 per cent greater than a reading obtained without water present. From the quality response curve previously obtained such a sensitivity could be expected from a radiation of mean energy 400 kV. Finally these measurements were related to measurements obtained in air by using a discrete 70 mg radium source placed at distances along the probe axis. This gave a calibration curve which could readily be checked at intervals throughout the period of clinical investigations.

It was obvious that a more satisfactory probe unit could be designed which would give a flatter quality response curve, e. g. anthracene crystal. This possibility was investigated when the probe had been in clinical use for some time and although with the anthracene crystal the spectral response was improved, the sensitivity was not as good. It was considered better to continue with the existing apparatus rather than alter the instrumentation in the middle of the clinical series. The checks and calibrations suggested that the probe readings could be taken as a measure of dose rate in r/hr. It must, however, be pointed out that the exact disposition of sources with respect to the crystal was not known in the majority of cases and therefore there may have been small changes in sensitivity due to directional and quality effects. The apparatus used would, we feel, give a reasonably good indication of true dose rate in the rectum.

Clinical measurements. Radium or cobalt insertions were carried out under general anaesthesia in the usual manner, and where radium was inserted into the vagina tight packing was used to increase the distance between ovoids and anterior rectal wall. The probe was inserted into the rectum to its full extent, with the patient in the lithotomy position. Leg clamps were then released and the legs fully extended so that the radium sources should occupy a position approximating to their relationship to the rectum with the patient in bed. Moreover, the probe readings were some 10 per cent higher with the patient in lithotomy than in the normal supine position. The probe was withdrawn slowly, the position of the crystal with respect to the anus being noted from the graduations on the probe, and the dose rate recorded. Tilting the probe within the lumen of the rectum it was possible to exert slight pressure on the anterior wall. The position of maximum dose rate occurred on average 11 to 12 cm from the anus, when ovoids and intra-uterine tube were used, and at a distance of 12 to 14 cm for Co^{60} sources in the uterus. A typical dose rate distribution along the rectum is shown in Fig. 1. Measurements were made at each radium or cobalt insertion and the mean of the maximum readings of dose rate were recorded for each particular patient. The total treatment time for each patient within a group was the same, so that the dose rate information obtained by measurement could be interpreted directly in terms of total dose.

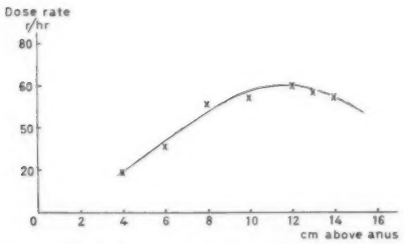

Fig. 1. Typical variation of dose rate with distance along the rectal mucosa from a full Stockholm case of 2 × 30 mg ovoids and 1 × 50 mg intra-uterine tube. Distance measured from the anus in cm.

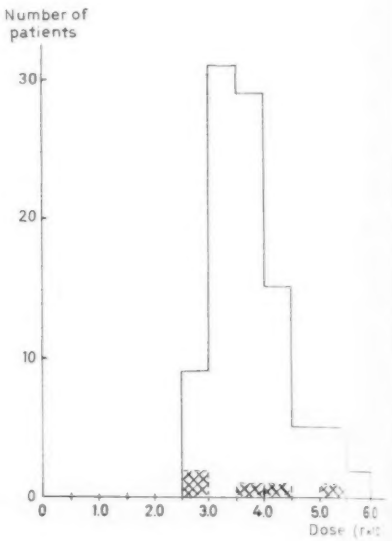

Fig. 2. Histogram presentation of the maximum rectal dose measured on 98 cases having 2 × 30 mg ovoids and 1 × 50 mg tube in situ. Mean dose rate 55 r/hr ± 13, mean dose 3 620 r ± 860. Incidence of proctitis 5 % of cases.

Results and observations

Damage to the rectum in radium treatment of carcinoma of the cervix has been discussed by one of us elsewhere (STRICKLAND 1954). Post-radium reaction is defined as a syndrome starting generally within 18 months of treatment and characterised by indefinite rectal pain or discomfort, intermittent diarrhoea, tenesmus and the passage of blood and mucus. It is not to be confused with the acute diarrhoea and rectal discomfort which occurs frequently towards the end of any course of radical irradiation where bowel is included within the irradiated volume. The mucous membrane in these cases is red and engorged and is sometimes covered by a yellow membrane but the appearances are quite different from those of post-radium proctitis. Moreover, the symptoms abate rapidly and are not followed by late bowel damage.

More often than not post-radium damage is self limiting and most cases go on to spontaneous resolution. A minority of cases become chronic and after a variable period rectal stricture occurs. As this stricture is usually partial, obstructive symptoms are uncommon, but occasionally chronic large bowel obstruction may be severe enough to demand colostomy.

During the acute phases, the classical appearances of 'radium proctitis' are seen. These are described in the standard textbooks on proctology and will not be repeated now. In a few cases massive local induration of the anterior wall of the rectum occurs, giving so-called 'pseudo-carcinoma'. Even this

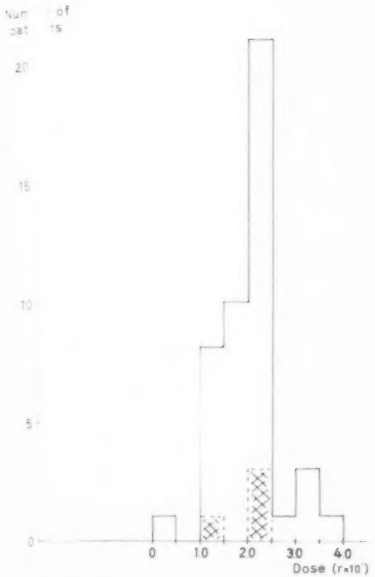

Fig. 3. Histogram-maximum rectal dose in 45 cases treated for carcinoma of body of uterus using intracavitary Co^{60}. Mean dose rate 45 r hr ± 8. Mean dose 2 160 r ± 384. Incidence of proctitis 10 % of cases.

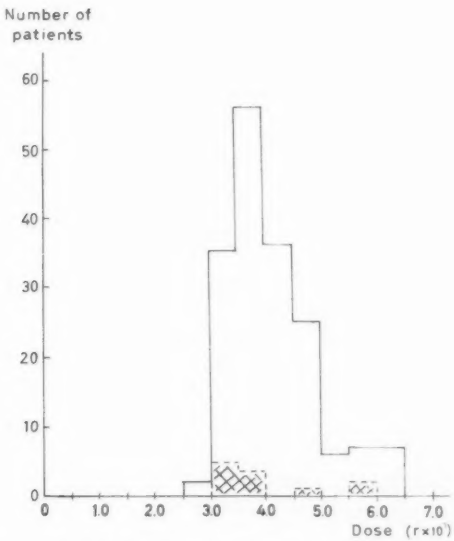

Fig. 4. Histogram-maximum rectal dose in all cases treated with intracavitary radium or cobalt for carcinoma of cervix and carcinoma of body of uterus. Total 169 cases. Mean dose 3 500 ± 580 r. Dose-rate dependent upon treatment technique. Incidence of proctitis 2 %.

tends to resolve in time but very occasionally fistulous communication may take place between rectum and vagina, or rectum and body of uterus, or both.

In this series, specific inquiry was made about any of the symptoms in which we were interested. In suspicious cases sigmoidoscopy was performed and the diagnosis confirmed visually. No other pathologic cause for the syndrome was encountered in this group, but where a history suggestive of rectal reaction was elicited and, for a variety of reasons the patient could not be admitted to hospital for clinical confirmation, the case was listed as a rectal reaction.

By this means we feel confident that the number of reactions recorded is, if anything, higher than the true number. However, a number of our patients died before they had time to develop a reaction so that this probably evens things out in a reasonable clinical way.

Group 1. The first group of 98 cases were patients having the modified Stockholm technique, two 30 mg vaginal ovoids, and one 50 mg intra-uterine

tube. The ovoids have a lead plug at one end which serves to reduce the dose to the rectum if the ovoid is correctly positioned. The radium was left in situ for a total period of 66 hours, the treatment being carried out in three equal sessions of 22 hours with an interval of seven days between each. Measurement of dose rate on the anterior rectal wall and the clinical assessments were made as described. The results are presented in Fig. 2. Of the 98 cases measured there was a 5 per cent incidence of rectal reaction and the mean dose rate to the rectal wall was 50 to 60 r/hr.

Group II. These were treated by intracavitary Co^{60} for carcinoma of body of uterus. All the sources were within the uterus and the position of maximum dose rate along the anterior rectal wall was further up the rectum than it was in the previous group. The mean dose rate lies between 40 to 50 r/hr (Fig. 3) and the treatment time was nominally 48 hours, corrections being necessary for Co^{60} decay. There is a 10 per cent incidence of rectal reaction — slightly higher than the previous group — the total dose to the rectal wall being somewhat lower than it was in the previous group.

Group III. There was a small group of cases consisting of patients having partial Stockholm treatment by tube or ovoid only. The group was too small to analyse statistically but one important observation was noted, namely that the total dose to the rectum in the modified Stockholm technique can be considered to be one third from the intra-uterine tube and two-thirds from the ovoids.

All cases. In Fig. 4 the total of 169 cases are presented and the figure clearly shows a negative correlation between high dose and the incidence of rectal reaction.

Conclusions. Rectal damage would appear to depend on some factor in addition to the dose level to which the rectum is raised during the course of treatment. The dose to the rectum was not confined to a small area of mucosa and the shape of the dose distribution along the anterior rectal wall was very similar in all patients investigated; statistically the incidence of rectal reaction in this series is not very high, but the distribution of the series indicates that high dose alone was not the cause of rectal symptoms.

SUMMARY

Description of a method of measuring dose rate on the anterior rectal wall of patients undergoing intracavitary treatment for uterine cancer. A scintillation probe with a sodium iodide crystal with suitable instrumentation, allowing the direct reading of the gamma dose rate, is employed. No positive correlation between high dose and rectal reaction could be observed in measurements on a material of 169 cases.

ZUSAMMENFASSUNG

Eine Methode zur Messung der Dosisgeschwindigkeit an der Vorderwand des Rektum von Patienten wird beschrieben, mit welcher eine intrakavitäre Behandlung eines Gebärmutterkarzinomes erhalten wird. Eine Scintillationssonde mit einem Natriumjodidkristall mit geeigneter Instrumentierung, die eine Direktmessung der Gammastrahlendosisgeschwindigkeit erlaubt, wurde benutzt. Bei Messungen in 169 Fällen konnte keine positive Korrelation zwischen hoher Strahlendosis und rektaler Reaktion beobachtet werden.

RÉSUMÉ

Les auteurs décrivent une méthode de mesure du débit de dose à la paroi antérieure du rectum chez des malades soumises à un traitement intracavitaire pour cancer du col de l'utérus. Ils ont utilisé une sonde à scintillations à cristal d'iodure de sodium, avec l'instrumentation appropriée, permettant la lecture directe du débit de dose gamma. Les mesures effectuées sur 169 cas n'ont pas mis en évidence de corrélation certaine entre les hautes doses et les réactions rectales.

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OPTIMAL TIME FOR MARROW INJECTION IN MICE AFTER TOTAL BODY IRRADIATION

by

BERTIL UNSGAARD

Lethal doses of ionizing radiation in mice produce within a week nearly total depletion of the blood-forming tissues. Dilatation of sinusoids and cell necrosis including pyknosis and karyolysis of nuclei are among the early changes observed in the bone marrow. Pancytopenia is thus produced and is usually complicated by infection and hemorrhages until anemia brings about the death of the animal. The protective action of spleen-shielding in mice, during exposure to whole body roentgen irradiation or of infusions of hematopoietic cells after irradiation, has been recognized since 1949 (JACOBSEN et coll.). In 1951, JACOBSON reported that transplantation of isologous spleens into the peritoneal cavity of mice within half an hour of exposure to 1 025 r total body roentgen irradiation increased the survival rate from 2.3 per cent in the control group to 50 per cent in the experimental group. The hematopoietic recovery was complete after 8 days. If the implantation was delayed one or two days after the irradiation, only 16.6 per cent survived 28 days. The bone marrow was unfortunately not examined in these cases. By reason of its hematopoietic capacity the spleen has in mice the ability to take over the function of the damaged bone marrow. Spleen-shielded mice not only

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sh[illegible] an abundant hematopoiesis in the spleen but also an early recovery of th[illegible] damaged bone marrow. Shielding of the bone marrow or other hemato-po[illegible]ic tissues has the same effect as transfusions of autologous bone marrow (J[illegible]OBSON 1952).

[illegible]RENZ et coll. (1951) indicated that in mice a suspension of isologous bo[illegible] marrow, given intravenously or intraperitoneally within 30 minutes of a [illegible]hal dose of roentgen irradiation, reduced the mortality from 100 per cen[illegible] in the control group to 25 per cent in the other two groups. In a later stu[illegible], approximately the same amount of bone marrow cells gave a good pro[illegible]ctive effect in spite of a delayed injection 4, 32, or 48 hours following the [illegible]radiation (LORENZ et coll. 1952); after 72 hours only a limited amount of p[illegible]otection remained and the mortality was as high as 73 per cent. It is, how[illegible]ver, remarkable to find the same number of dead animals when the injec[illegible]n was given 24 hours after the exposure.

The sensitivity to ionizing radiation fluctuates in different strains of mice. Gen[illegible]tic conditions exist for this, according to a paper published from the Research Institute of National Defence (See FRÖLÉN et coll.). The resistance is not only a result of dominant genes but also of additive or recessive genes. Treatment with hematopoietic cells at the time of total body irradiation does not give the same result: for instance, in some strains, good protection was observed after intraperitoneal injection but not in others (LORENZ et coll. 1952, CONGDON 1957).

The present investigation was performed in order to find out the optimal time for the marrow injection in our CBA strain, which is reported to be resistant to irradiation. The intention was also to compare the early as well as the late treatment of bone marrow with Tyrode's solution.

Materials and Methods

Animals. Nine hundred and eighty male mice of a CBA strain (imported into Sweden from Dr. T. C. Carter in Harwell) were used in this investigation. This strain is inbred by brother-sister mating in 130 generations the last ten being mated in Stockholm. The animals were all 9 weeks old when the study started, and weighed between 22 and 26 g. Commercial cubed food and tap water were available in excess.

Radiation factors. The roentgen source was a Müller MG 300 unit, operated at 260 kV and 10 mA; filter 0.5 mm Cu, inherent filtration 4 mm Al; dose rate 84 r/min, measured with a Moxnes' electrometer and a Sievert condenser chamber; FOD was approximately 40 cm. The animals were irradiated with 1 092 r to the whole body. Ten mice were kept in a plastic container, divided into ten compartments, and irradiated simultaneously. In order to obtain uniformity of dosage the plastic wheel was rotated during the exposure at 1 rpm. The irradiation was accomplished under mebumal anesthesia (each animal received 0.0015 g intraperitoneally) so as to avoid fracture of the neck during the relatively long (13 minute) exposure. After the irradiation the mice were pooled and placed at random in the cages, ten to each cage. The number of dead animals was counted twice a day during the 30 days.

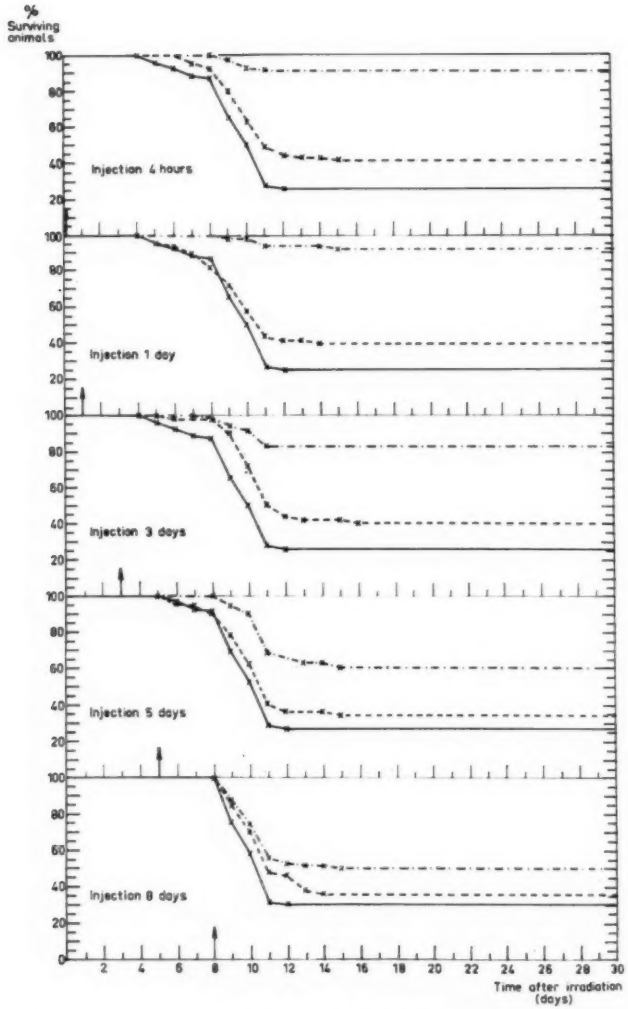

Fig. 1. Time-survival curves for mice which after total body irradiation received injection, in 5 groups at different times, of isologous bone marrow (—·—·—), or Tyrode's solution (— — — —), and for a control group (——) which received no injection.

Bone marrow suspension. The bone marrow was collected from the femoral bones of tw e-to-thirteen-week-old CBA mice of both sexes. The bones were cleaned thoroughly fron d-hering tissue. A needle was inserted in the lower end of each femur, the collum femori as

Table 1

The 30-day mortality, f, in the different cages

	K	M_4 hours	M_1 day	M_3 days	M_5 days	M_8 days	T_4 hours	T_1 day	T_3 days	T_5 days	T_8 days
	0.6	0.0	0.2	0.1	0.5	0.6	0.7	0.4	0.6	0.8	0.6
	0.9	0.1	0.1	0.2	0.7	0.3	0.6	0.5	0.6	0.6	0.7
	0.7	0.0	0.0	0.3	0.2	0.8	0.5	0.6	0.6	0.7	0.7
	0.7	0.2	0.0	0.1	0.3	0.5	0.6	0.8	0.4	0.4	0.6
	1.0	0.1	0.1	0.2	0.2	0.6	0.8	0.7	0.8	0.8	0.6
	0.6	0.1	0.1	0.1	0.2	0.2	0.5				
	0.7	0.1	0.0	0.2	0.7	0.5	0.4				
Mean frequency	0.74	0.09	0.07	0.17	0.40	0.50	0.59	0.60	0.60	0.66	0.64

cut off and the medullary canal perfused with Tyrode's solution without heparin. During the preparation the container with the suspension was placed in a water bath of 5° C. In order to eliminate clumps of bone marrow, the suspension was squeezed through a series of No. 12 to No. 20 gauge needles. The marrow (at 37° C) was injected quite fresh or within half an hour after its preparation, each animal receiving 0.5 ml of the suspension intraperitoneally. The number of living cells injected were estimated at approximately 20×10^6 after standardization of the suspension. The counts were made in a haemocytometer on eosin-resistant cells. The animals were divided into three groups: those which received bone marrow (M), those which received pure Tyrode's solution (T), and the control animals (K).

Results

The same amount of isologous bone marrow, on an average 20×10^6 nucleated cells, was injected intraperitoneally into CBA mice, in separate groups five different times after 1 092 r of total body roentgen irradiation. The 30-day survival within the different groups is shown in Fig. 1. A comparison of the curves indicates that the mortality within the marrow groups increases with the interval of time between the total body irradiation and the treatment, while the mortality is unchanged in the groups treated with Tyrode's solution. The survival is, however, identical in the two groups where the bone marrow was given after 4 and 24 hours (91 and 93 per cent). The animals treated with marrow die later than those not so treated except when the injection is given 8 days after the irradiation.

The cages were used as units in this investigation, the mortality being observed in every cage (Table 1). The frequency of mortality of the different cages, f, has been treated statistically and in order to handle this material more conveniently the frequencies have been transformed according to the well-known formula $y = 2 \arcsin \sqrt{f}$ (Table 2). At the frequencies 1 and 0, the Bartlett correction has been employed which means that frequency 1 is interpreted as if 1/4 animal had survived and frequency 0 as if 1/4 animal

Table 2

The transformed 30-day mortality, y, according to the formula $y = 2 \arcsin \sqrt{f}$ ***

	K	M_4 hours	M_1 day	M_3 days	M_5 days	M_8 days	T_4 hours	T_1 day	T_3 days	T_5 days	T_8 days
	1.77	0.32	0.93	0.64	1.57	1.77	1.98	1.37	1.77	2.21	.77
	2.50	0.64	0.64	0.93	1.98	1.16	1.77	1.57	1.77	1.77	.98
	1.98	0.32	0.32	1.16	0.93	2.21	1.57	1.77	1.77	1.98	.98
	1.98	0.93	0.32	0.64	1.16	1.57	1.77	2.21	1.37	1.37	.77
	2.82	0.64	0.64	0.93	0.93	1.77	2.21	1.98	2.21	2.21	.77
	1.77	0.64	0.64	0.64	0.93	0.93	1.57				
	1.98	0.64	0.32	0.93	1.98	1.57	1.37				
y	2.11	0.59	0.54	0.84	1.35	1.57	1.75	1.78	1.78	1.91	1.85

* The 95 per cent confidence intervals for $\bar{y}$, are for the first seven columns
(K—T_4) $\bar{y} \pm 0.24$
and for the last four columns
($T_{1\ day}$—$T_{8\ days}$) $\bar{y} \pm 0.29$

Source of variation	Degrees of freedom	Sum of squares	Mean square
Treatments.....	10	20.3	2.03
Exp. units within treatments	58	6.07	0.105
Total	68	26.37	

$$F = \frac{2.03}{0.105} = 19.3$$

had succumbed (BARTLETT 1947). By means of this transformation a variance independent of the y-value is obtained. The expected value of this variance is 1/n (where n is the number of animals in each unit), that is in this case 1/10. The y-variable shows a distribution that follows quite close to the normal distribution. The conditions for an analysis of variance are in this way fulfilled.

The variance within the treatments in the analysis was 0.105, that is to say almost exactly the expected value 1/10. The variance between the treatments was 2.03. The quotient of variance, 2.03/0, 105 = 19.3, indicates a strongly significant difference between treatments.

It is possible to make some independent comparisons between the different treatments, the most interesting being between early M-treatment (M_4 hours + M_1 day) and early T-treatment (T_4 hours + T_1 day), and between late M-treatment (M_5 days + M_8 days) and late T-treatment (T_5 days + T_8 days). The former is strongly significant and even the latter indicates a clear significance (Fig. 2).

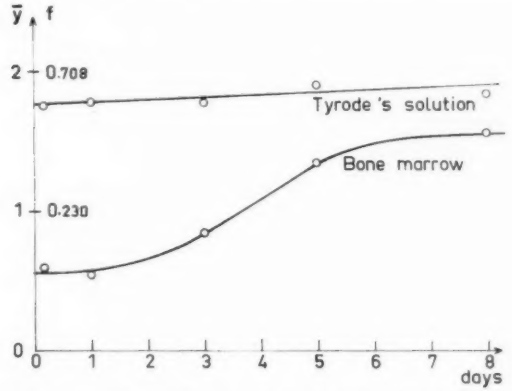

Fig. 2. The 30-day mortality, f, and the transformed 30-day mortality, y, in relation to treatments with isologous bone marrow or Tyrode's solution at 4 hours, 1 day, 3 days, 5 days and 8 days after irradiation.

Early treatment 4 hours + 1 day	Late treatment 5 days + 8 days
Mf 0.08	Mf 0.45
Tf 0.59	Tf 0.65

The relation between the 30-day survival in the control group (K), and the different groups treated with Tyrode's solution (T), is also significant. This is, however, not valid between the T-groups.

Discussion

During the whole study the suspension was administered intraperitoneally, though injections given intravenously are considered to have a better and a more rapid effect on the blood-forming tissues and, consequently, also on the circulating blood (LORENZ et coll. 1952). In a pilot test on female CBA mice, 9 weeks old, the same percentage of survival was found by experiment in the two groups as shown in Fig. 3. In this test approximately the same number of isologous bone marrow cells, 20×10^6, were injected 24 hours after exposure to 1 092 r total body irradiation. This number of cells may explain the good result and account for the success of that part of the test where the injections were made intraperitoneally.

The given dose of irradiation has been mentioned as approximately an LD_{10} 30 days. In this material the mortality reached 74.3 per cent in the control group which received no treatment after the irradiation. The explanation for this may lie in the fact that the animals were anaesthetized during

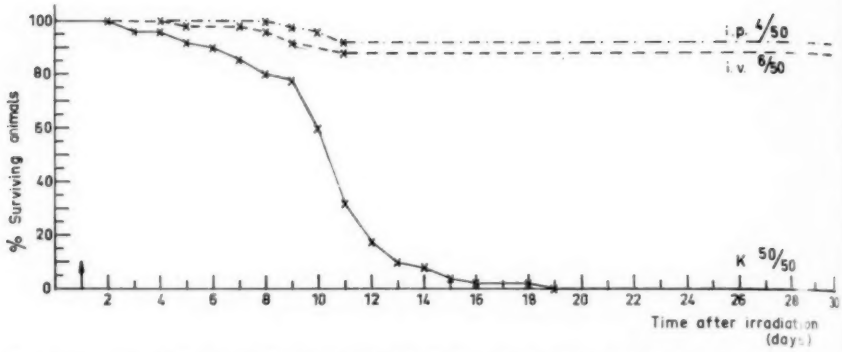

Fig. 3. Time-survival curves after total body irradiation with subsequent injection of isologous bone marrow intravenously or intraperitoneally (K = control animals).

the exposure through which their metabolism was diminished (LORENZ et coll. 1954), and also that they escaped the stress associated with being confined in the container. In another experiment going on simultaneously the 30-day mortality was 97 5 per cent in the control group. The animals and the conditions for irradiation were exactly the same except that they were conscious during the exposure.

The animals died between the 5th and the 16th day, with a maximum of 70 per cent during the 9th to the 11th day. Nineteen animals died during the 5th day. The corresponding number up to the 8th day inclusive was 67. The majority of these animals died in connection with the injection on the 5th or the 8th day after the irradiation. Large subcutaneous hemorrhages were often found in the back of the head and round the site of injection. The purpose of this investigation was to prove the effect of a suspension of bone marrow, as compared with pure Tyrode's solution, injected in groups of equal numbers of animals at five different times after the exposure. All the animals which died before the treatment, including all which died immediately after the injection, were substituted from reserve cages which had been irradiated at the same time and in the same manner as the original cages of the experiment. Twenty reserve animals were assigned to each of the seven days of experiment. The animals were taken out at random. This procedure explains the fact that the curves start from 100 per cent even when the injection was given 5 or 8 days after the irradiation. A selection of animals is thus inevitable for the late treatment. This is, however, unimportant, particularly for the reason that a comparison is made between the simultaneous M- and T-treatments. The control animals were favoured as they were never unnecessarily touched in the cages after irradiation.

During the first two days after irradiation it is usually impossible to notice any external signs referable to the procedure. Several animals acquire during the third day a rough coat. From the 5th day all animals are remarkably inactive. They grow more or less thin and show signs of dehydration. Distinct dorsal kyphosis appears. The feces are of a cream-like consistency and often give a positive benzidine test. The signs progress further and reach a maximum between the 9th and the 11th day. The mice treated with bone marrow within 24 hours after irradiation are considerably less affected during this period, as has been shown before (LOUTIT 1957). Animals not treated with bone marrow, and which survive, recover more slowly than the marrow-treated animals.

It seems strange that the mortality in the different groups treated with Tyrode's solution is nearly exactly the same. This was considered to be due to the fact that several reserve animals were put in the groups with late treatment. A repetition of this part of the experiment was made. On this occasion no animals died before the injection. The result was the same. The effect of Tyrode's solution seems to consist in the supply of fluid.

The survival among the irradiated animals bears a direct relationship to the return of the blood-forming tissues to a normal state (CRONKITE et coll.). The number of bone marrow cells injected decide the survival of lethally irradiated mice; doses above 12×10^6 cells give optimal protection (URSO & CONGDON, VAN BEKKUM & VOS). The great number of animals in this experiment admit a very accurate, statistically guaranteed, determination of the effect of bone marrow at the five different times of infection. This study which is intended to form a basis for further investigation on CBA mice confirms what has previously been found, viz., that the optimal time of infusion of bone marrow is at 4 hours after irradiation. It also shows that the same result is obtained 24 hours after the exposure The marrow cells have, however, still a certain effect on the 5th and on the 8th day after the irradiation.

Acknowledgements

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SUMMARY

Mice of the CBA strain, 9 weeks old, were divided in five separate groups and treated with an intraperitoneal infusion of isologous bone marrow at different times after a lethal dose of total body irradiation. The results show that the optimal time for the infusion of bone marrow is within 24 hours of the irradiation. A certain effect still remains, however, on the 8th day after the dose.

ZUSAMMENFASSUNG

Mäuse des CBA-Stammes wurden nach einer Totalbestrahlung mit lethaler Dosis in fünf Gruppen verteilt und mit einer intraperitonealen Einzelinfusion isologen Knochenmark zu verschiedenen Zeitpunkten behandelt. Die Ergebnisse zeigen, dass der optimale Zeitpunkt für die Infusion des Knochenmarks innerhalb von 24 Stunden nach der Bestrahlung liegt. Ein gewisser Effekt ist jedoch noch am 8 Tage nach der Dosis vorhanden.

RÉSUMÉ

Des souris de la lignée CBA, âgées de 9 semaines, ont subi une irradiation de tout le corps à dose léthale; elles ont été réparties en cinq groupes qui ont été traités, à des dates différentes après l'irradiation, par une injection intrapéritonéale de moelle osseuse isologue. Les résultats montrent que le moment optimum pour l'injection de moelle osseuse se situe dans les 24 heures qui suivent l'irradiation. Le traitement fait le huitième jour après l'irradiation a cependant encore un certain effet.

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DOSE FACTORS AND MORPHOLOGY OF DELAYED RADIATION LESIONS OF THE INTERNAL AND MIDDLE EAR IN RABBITS

by

NILS O. BERG and MARTIN LINDGREN

A previous investigation of the effect of roentgen irradiation on the brain in rabbits showed that vestibulo-cerebellar signs were very common (BERG and LINDGREN 1958). This has prompted an analysis of the dose factors and the morphology and site of lesions after roentgen irradiation in single doses as well as fractionated doses to one half of the head of the rabbit. This forms the subject of the present communication.

Labyrinthine signs not verified histologically. The effect of ionizing radiation on the ear was demonstrated as early as in 1905 by EWALD. A glass ball containing about 3 mg radium bromide placed in the region of the labyrinth for some hours (the species of animal used was not mentioned) produced after some days signs that were of the same type as those occurring after extirpation of the labyrinth, such as turning of the head. The severity of the signs varied with the irradiation time.

HABERSTÄDTER (1920) reported that after mice had been submitted to protracted roentgen irradiation of one side of the skull they ran around in circles with the irradiated side innermost; the animals died a few hours later (cit. THIEMANN).

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Russel, Wilson and Tansley (1949) described vestibulo-cerebellar gns after roentgen irradiation of one half of the rabbit's head from above ith 2 850 and 2 440 r (single doses at 200 kV). These were interpreted as r ni- festations of damage to the CNS.

Gerstner, Pickering and Dugi (1955) gave a detailed description o the labyrinthine syndrome with turning of the head and 'manège movemen ' in the rabbit 6 to 100 hours after irradiation with a single dose of 12 000 r t the whole head. They stress the similarity of the signs with those referab to destruction of the labyrinth.

Abdullin (1957) observed delayed effects of roentgen irradiation of the ead in pigeons and rabbits with single doses of up to 2 500 r in the form of m ked postural disturbances such as opisthotonus, turning of the head to one ide, forced rotatory movements, etc (cit. Livanov and Biryukov 1958).

Labyrinthine signs with morphologic lesions verified histologically. Marx (909) irradiated 15 pigeons with 4 mg radium placed in the right aditus to the ym- panic antrum for 30 minutes to 2 hours. After a varying interval some of the animals showed typical labyrinthine signs. Microscopic examination 2 weeks to 12 months after exposure revealed degenerative and atrophic chang s in the sensory epithelium of the vestibule and crista ampullaris. The degree of these histologic changes did not vary with the duration of the exposure.

Marx also placed 4 mg radium near the apex of the cochlea in the middle ear for 1 hour in 7 guinea pigs. Six animals showed no obvious response, while the seventh had typical signs of vestibular damage. Histologic examination after 2.5 to 6 months revealed changes in all the animals, similar to those in the pi- geons, as well as destruction of the organ of Corti, the spiral ganglion and the cochlear nerve, though the changes were less marked in the animal with no signs. He claimed that variation in the position of the radium might have been responsible for the differences in the appearances. He was apparently the first to have pointed out the significance of the latency before the appearance of damage by ionizing radiation.

Chilow (1927) placed a glass ampoule containing radium emanation into the tympanic cavity of cats in order to exclude the action of the otoliths. Three cats were irradiated, one with a dose of 13.5 mC and the others with 4 mC. After 3 days the first animal exhibited marked vestibular signs and died after a week; the other 2 animals showed only slight disturbances of function. Any difference in the duration of nystagmus capitis between the two sides was regarded as an effect of irradiation. Microscopic examination revealed co- agulated lymph in the scala tympani and vestibuli and a varying degree of leukocytic infiltration. In the first cat haemorrhages were evident as well as degenerative changes of the sensory cells of the type described by Marx (909).

Thielemann (1929) contributed an important analysis of the ra ation damage to the internal and middle ear in mice. Soon after roentgen irra iation

the animals presented typical labyrinthine signs and intense hyperaemia, and punctate haemorrhages in the internal ear, middle ear and auditory nerve; these were followed somewhat later by a serous or seropurulent inflammation of the middle ear and eventual fibrosis.

The lowest doses producing changes were a single dose of 8 to 9 HED, or a total of 12.8 to 14.6 HED given in two doses at 4 to 5 weeks intervals against the whole head alternating from above and the side. The technical data are incomplete but, according to the author, one HED corresponds to 500 r.

Signs did not usually appear until after the second exposure. The animals died spontaneously or were killed a few days following the onset of signs. The first sign, which was observed 24 to 36 hours after irradiation, was hyperacusia. Later, diarrhoea and loss of bodyweight occurred and the general condition deteriorated. Three mice had disturbances of equilibrium with forced rotatory movements; the ear reflexes had disappeared in several of the animals.

Histologic examination the first few days after irradiation showed intense hyperaemia in the entire region of the ear as well as in the cerebral meninges. In animals with signs referable to the internal ear, punctuate haemorrhages, particularly perilymphatic, were present in the vestibule as well as in the auditory nerve, middle ear and tympanic membrane. No inflammatory reaction was observed at that stage. The haemorrhages were often related to the vessels, for instance cochlear haemorrhages at the vena canaliculi cochleae, although no direct vascular damage was observed. It was not until the ninth day that any serous or seropurulent otitis media with oedema and punctate haemorrhages in the mucosa were observed. The epithelium was then shed and the exudate became purulent. No complications due to sepsis occurred. In one animal examined 83 days after being irradiated with 6.8 HED the middle ear had a thickened mucosa with loose fibrosis extending around the auditory ossicles.

This brief survey suggests that disturbances of function and morphologic changes may be produced in the labyrinths of experimental animals by radium and roentgen rays. Negative results have, however, also been reported. Thus NOVORNY (1951) found no impairment of hearing or histologic changes in 6 guinea pigs examined 6 weeks after single irradiation with a dose of 1 000 to 7 200 r.

The effect of radium irradiation is difficult to judge because the seeds used may produce mechanical lesions. In a review published in 1931 DESJARDINS adopted a critical attitude towards these examinations. On the other hand, the disturbances of function observed by THIELEMANN and others after roentgen irradiation have been confirmed by more recent investigators (RUSSEL et coll., GERSTER et coll.).

Knowledge of the relationship between the doses and morphologic lesions, and particularly of the highest dose tolerated without observable damage, is thus far from complete.

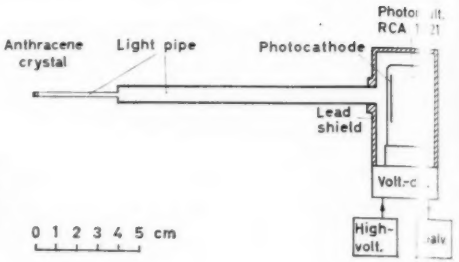


Fig. 1. Scintillation dose-rate meter for point measurements. Sensitive anthracene crystal 1.5 mm long and 1.2 mm in diameter. Tube with a highly polished inner wall as 'light pipe'.

Material and Methods

Material. Seventy-nine rabbits were obtained in litters of two to five, most of the animals belonging to litters of 4 animals. Each experimental group was made up of 10 rabbits selected from the different litters in such a way that the mean weight per group was as uniform as possible; these mean weights varied between 2.20 and 2.39 kg. The animals were observed for 52 weeks following the end of treatment. For doses used in different types of treatment, see Table 4.

Technical data. Müller roentgen apparatus MG 300; 200 kV constant potential, 10 mA; filter 0.5 mm Cu + 1 mm Al; half-value layer for the quality of the radiation was 0.93 mm Cu; dose rate 105 r/min in air; FSD 25 cm; surface dose 117 r/min.

The roentgen beam was focused over the right half of the skull, the left side being shielded with 3 mm lead; the hole in the 1 mm mask measured 30 × 40 mm. The central ray passed through the centre of the field.

Dosimetry. The depth doses delivered to the rabbit's brain by this method have been previously described (Berg and Lindgren 1958). The isodose diagram (Fig. 2 a), however, holds only for the central parts of the brain; these are covered only by the calotte, which is about 1 mm thick and may be neglected as far as radiation absorption is concerned. The internal ear, on the other hand, is enclosed in a thick layer of bone, and is situated about 1.5 cm behind the central parts of the field. The depth dose was therefore measured directly.

The heads of 2 rabbits (weight 2.3 kg), which had been prepared by the arterial injection of 10 % formalin were used. The skulls were sawn horizontally 16 and 25 mm respectively below the vertex over the irradiated area. Radiation data: 175 kV, 2 mA, 0.5 mm Cu + 1 mm Al, giving a half-value layer of 0.95 mm Cu, FSD 35 cm, and field size 30 × 40 cm. The measurements were made with a scintillation dosemeter (Fig. 1) constructed by Lidén and Larsson (1960).

Three measuring points were selected: one in the medulla at a depth of 25 mm and 3 mm from the midline of the skull (B_1), one situated in the floor of the middle ear at the same depth but 5 mm from the midline (B_2), and a third point 16 mm below the vertex and 11 mm from the midline in the paraflocculus of the cerebellum (A), i. e. at the level of the upper semicircular canal (Fig. 2b). The dose delivered to each point and the corresponding skin dose were measured twice, and the values obtained at the individual depths showed good correlation. The mean value found for each depth dose was corrected for FSD 25.0 cm.

The dose at a depth of 16 mm was 77 % and at 25 mm 59 % (the same at 3 and 5 mm from the midline). These values are compared in Fig. 2a with those earlier obtained for the rabbit's brain. It was found that the dose at the upper measuring point was only 2 % lower

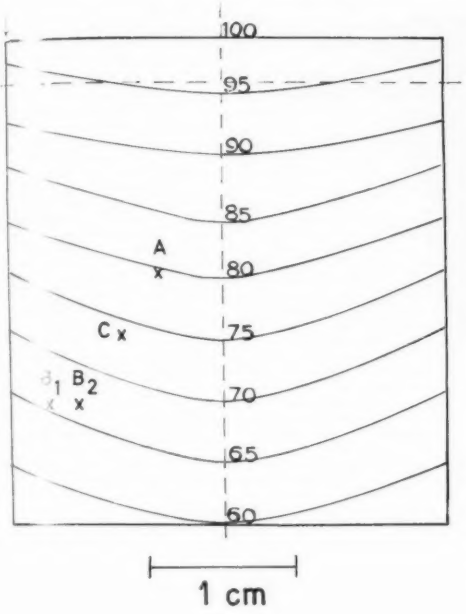


Fig. 2a

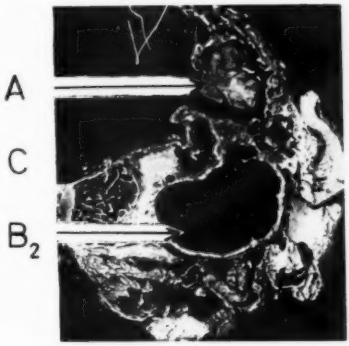


Fig. 2b

Fig. 2. a) Experimentally determined dose in region of ear (A, B_1 and B_2) in relation to isodose curves in transverse section through centre of field. Interrupted line indicates upper surface of brain and arrow midline of brain. C = interpolated dose at middle of labyrinth. b) Approximate position of measuring points in a section through the ear.

and at the lower point about 7 % lower. The deviation may be explained by the effect of absorption of the radiation in the thick bone around the cerebellum and the inner ear. The dose at the centre of the internal ear, which lay intermediate between the 2 measuring points and 8 mm from the midline, was extrapolated and a value of 68 % with a range of 61 % to 75 %, according to the size of the labyrinth, was obtained. The depth doses corresponding to the skin doses in the experimental groups are given in Table 4.

Results

General and neurologic signs. Animals irradiated with higher doses (3 000 to 2 500 r single dose, 6 500 r/12 days or 10 500 r/30 days) often showed characteristic signs during the observation period. These appeared as a rule between the 15th and 40th week following the end of treatment. Many of the animals gradually lost weight, their general condition deteriorated, and twenty were killed before the end of the observation period. The frequency of the various signs in the individual groups is given in Table 1. No signs were observed in two groups (5 400 r/12 days and 6 600 r/30 days).

A clear correlation was found between the size of the dose and the frequency and time of appearance of the neurologic signs; in the groups that received large fractionated doses (6 500 r/12 days or 10 500 r/30 days) changes in bodyweight were only moderate but neurologic signs were often noted.

Table 1

Frequency of signs in different groups (10 animals in each)

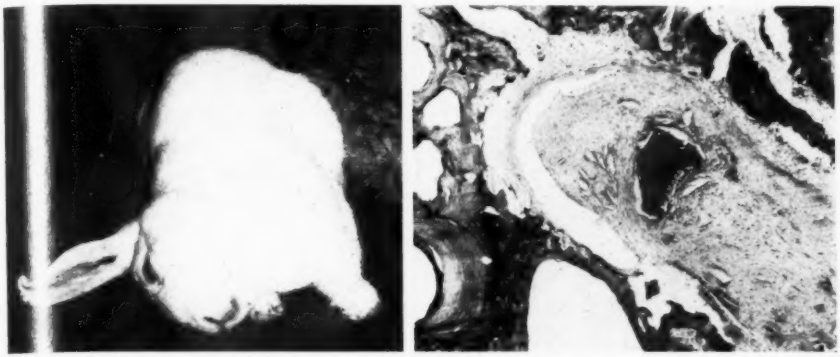
Signs	Single dose			Fractionation of d		
	3 000 r	2 500 r	2 100 r	6 500 r 12 days	10 500 r 30 days	8 8 r 30 ys
General						
Loss of bodyweight	7	5	—	3	5	–
Apathy and sopor	1	—	—	2	1	–
Death (unexpected)	—	—	2	—	—	–
Neurologic						
Vestibulo-cerebellar	8	4	—	5	8	–
Turning of head, temporary	2	1	—	1	1	–
» , permanent	6	2	—	3	7	–
Walking in circles	—	—	—	—	1	–
Disturbance of equilibrium	6	2	—	2	5	–
Nystagmus capitis	2	1	—	1	3	–
Rolling-over	4	3	—	2	3	–
Miscellaneous						
Irritability	1	3	—	—	1	–
Seizures	—	—	—	3	—	–
Paresis (temporary)	—	—	—	—	—	1
Inequal pupils	—	2	—	—	—	–
Loss of corneal reflex	1	—	—	—	—	–
No signs	1	4	8	5	2	7
Death before 52nd week	7	2	2	3	1	–

Vestibulo-cerebellar signs were most common. Oblique positioning of the head, which was tilted towards the treated side, appeared in 24 animals. The signs were sometimes first detected when the treated animals were gripped by the skin of the back and lifted; later they developed a permanent turning of the head of anything up to 90 degrees (Fig. 3a). In some animals this unnatural position of the head was transient, but where it was marked the animals usually lay on the right side and stumbled or fell when placed on their feet. Some of the animals with disturbances of equilibrium were less affected and could move about in their cages and eat without difficulty.

Neurologic signs of the cerebral type were occasionally evident, and mild transient paresis was observed in one animal. Three animals had epileptic seizures; these had co-existing vestibulo-cerebellar signs. Inequality of the pupils and loss of the corneal reflex were noted in a few animals.

Histo-pathologic findings

The type, extent and distribution of the cerebral lesions have been reported in detail in a previous paper (Berg and Lindgren 1958). The changes in the CNS were mainly of the same histologic type whether the animals received a



a b

Fig. a) Twenty-five weeks after end of irradiation with 10 500 r/30. The rabbit's head was tilted 90° to the treated side and the animal frequently rolled over on its side; nystagmus capitis and temporary loss of weight. b) From rabbit shown in (a). Fibrosis of middle ear with old hemorrhage at centre. Hollow spaces where cholesterol crystals have dissolved. Aseptic osteitis in bone walls with lacunar absorption. Haematoxylin and eosin. × 30.

single or a fractionated dose. Table 2 gives a survey of the morphologic findings; it is clear that the frequency of gross changes decreased with the dose irrespective of the type of treatment. The effect of a fractionated treatment of 10 500 r/30 days on the CNS was somewhat less than that produced by 2 500 r, but somewhat more than that following a dose of 2 100 r both in single doses. Some of the animals in the group that received 6 500 r/12 days had violent vestibulocerebellar signs with loss of bodyweight after 25 to 30 weeks, when the animals were killed. The survival of these animals was probably not long enough for any CNS changes to develop. A dose of 6 500 r/12 days thus has a greater effect on the CNS than 2 100 r in a single dose.

In addition to these frank cerebral lesions, discrete changes in the form of small foci corresponding to damage to the small vessels were evident in all the

Table 2

Distribution of marked cerebral lesions in different regions of CNS

Site of lesions	Single dose			Fractionation of dose				
	3 000 r	2 500 r	2 100 r	6 500 r 12 days	5 400 r 12 days	10 500 r 30 days	8 000 r 30 days	6 600 r 30 days
Hemispheres or basal ganglia	8	8	2	1	0	6	0	0
Mesencephalon	3	2	1	1	0	1	0	0
Cerebellum	9	8	0	0	0	2	0	0
Pons or medulla	5	0	0	0	0	0	0	0
Mean survival time in weeks	44	51	51	45	52	50	52	52

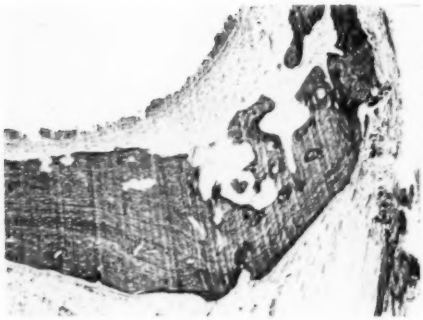


Fig. 4

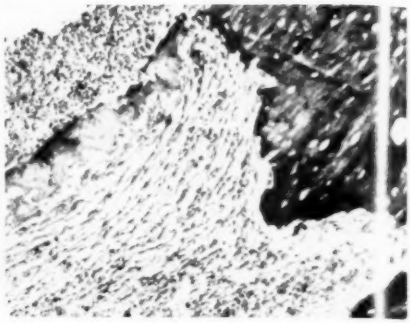


Fig. 5

Fig. 4. 10 500 r/30 days. Purulent otitis media with fibrous thickening of mucous membrane and advanced destruction of floor. Atrophy with fibrosis in insertion of the masticatory muscle (right lower corner). No lesions in internal ear but facial nerve necrotic. Peripheral lesions in nerves and musculature explain turning of the head to irradiated side. Van Gieson. × 75.

Fig. 5. 10 500 r/30 days. Necrosis of wall of middle ear secondary to purulent otitis. Van Gieson. × 190.

groups treated; these lesions were observed in the various groups and their distribution was such as to support the above-mentioned conclusions.

An analysis of the evaluation of damage to the internal ear and middle ear was made difficult by the high frequency of complications due to infection in some groups. The results of the histologic examination of these structures in the animals treated with 2 100 r and 3 000 r in single doses and 10 500 r/30 days doses are described in detail below.

Auditory canal, skull bone and soft tissues. In the 2 100 r group slight hyperplasia of the epithelium of the canal occasionally occurred. In the 3 000 r and 10 500 r groups the auditory canal was often filled with leukocytes and squamous epithelial lamellae, and the epithelium was hyperplastic. No cellular atypia was evident. In many cases the exudate originated from the middle ear and the ear drum was often perforated or thickened.

In a few cases small erosions of the epithelium in the auditory canal and abscesses in the surrounding soft tissues were evident. Four animals of the 3 000 r group had diffuse soft tissue changes, which were obviously related to the severe skin reactions with radionecrosis in which abscesses developed; these abscesses spread laterally and medially to the base of the skull and into the insertions of the cervical and the masticatory muscles. Considerable fibrosis was present around the abscesses together with osteitis which was particularly common in the walls of the auditory canal.

In the 10 500 r group the process was more fibrotic and widespread abscesses

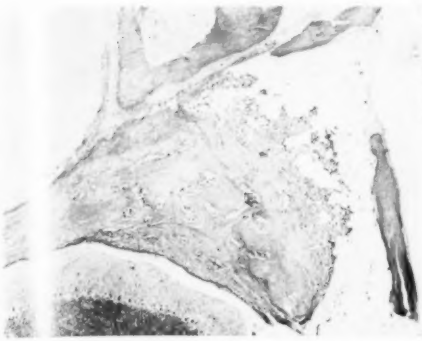


Fig. 10 500 r/30 days. Osteogenic sarcoma in bony wall between internal ear and paraflocculus of cerebellum. No vestibulo-cerebellar signs. H. & E. × 30.

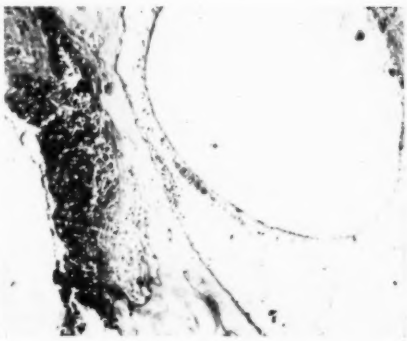


Fig. 7. From same rabbit as in fig. 5. Involvement of utricle of internal ear. H. & E. × 83.

were not evident. Fibrosis in the masticatory muscle was noted in a few rabbits (Fig. 4).

Bone changes were most marked around the auditory canal and the middle ear, even in the absence of skin necrosis and infection, in the 3 000 r and 10 500 r groups. The bone showed evidence of lacunar absorption and had been replaced by loose or fairly dense fibrotic tissue (Figs 3a, 4 and 5). Proliferative lesions developing in osteogenic sarcomas were also evident. In one of the animals that had received 10 500 r/30 days an osteogenic sarcoma infiltrated the occipital bone and the petrous bone (Fig. 6). Most of the animals in the 2 100 r group had only slight lacunar absorption and sclerosis of bone. One animal, however, had sclerosis of the occipital bone together with a circumscribed area of immature osteoid tissue with cell atypia (? early osteogenic sarcoma). In one animal that had received 2 500 r, a tumour with involvement of the internal ear and compression of the medulla, pons and cerebellum was evident. This tumour, which presented histologic features of an osteogenic sarcoma, had produced rapidly progressing vestibulo-cerebellar signs and a fatal issue.

Middle ear. Fibrosis and other changes were present in the walls of the middle ear in most of the animals in the 3 000 r and 10 500 r groups. In mild cases the mucous membrane was thickened and fibrotic, the fibrosis being loose; it lined the walls and the ossicles were frequently involved. The epithelium was atrophic. Very few inflammatory cells were present. In two cases the exudate was haemorrhagic (Fig. 3b). Purulent inflammation was noted in the more severe cases, the epithelium being often completely destroyed, the ossicles involved and lacunar absorption evident in the bony walls (Figs 4 and 5);

Fig. 8. 10 500 r/30 days. Rarefaction of cochlea and cochlear nerve; no evidence of inflammation. The rabbit survived the entire experimental period (52 weeks). H. & E. × 30.

Fig. 9. From same rabbit as in fig. 3. Rarefaction of macula of utricles with complete loss of sensory cells. Loss of myelin sheaths in vestibular nerve. Van Gieson. × 42.

the exudate was often purulent with an admixture of plasma cells and lymphocytes. The tensor tympani muscle was fibrotic and atrophic. No lesions were detected in the middle ear in the 2 100 r group.

Internal ear. Like the lesions in the soft tissues and the middle ear those of the internal ear could be divided into an aseptic and an inflammatory group.

Acute purulent labyrinthitis was demonstrated in 2 animals in the 3 000 r group with spread of inflammation from the middle ear in both cases. In one animal there was an apparently aseptic labyrinthine lesion. This animal had widespread soft tissue abscesses which were breaking down into the cerebellum. As fibrosis and osteitis were present in the middle ear an inflammatory origin of the lesion of the labyrinth could not be excluded with certainty.

One animal in the 10 500 r group had purulent otitis media encroaching upon the internal ear with purulent labyrinthitis (Fig. 7). Aseptic lesions occurred in 5 rabbits. The membrane of the utricle and saccule and of the semicircular canals was often wrinkled. An albuminous exudate with few inflammatory cells and occasional haemorrhage were found in and around the membranous labyrinth. In one animal with total necrosis of the auditory nerve rarefaction of the cochlea without inflammatory changes was observed (fig. 8). In 2 animals, the macula of the utricle was completely necrotic and the epithelial cells and the neural elements had been replaced by sparse vacuolized histiocytes (Fig. 9). Organisation with histiocytes and fibroblastic cell proliferation was evident and many histiocytes laden with Fe pigment were present in the perilymphatic space of the semicircular canals (Fig. 10). In one animal,

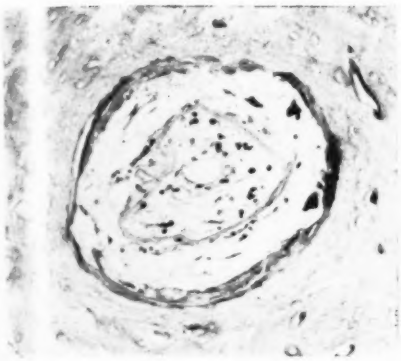


Fig. 10. 10 500 r/30 days. Destruction of membranous labyrinth with proliferation of loose fibrotic tissue and capillaries. Histiocytic cells with Fe pigment in perilymphatic space. Commencing new bone formation. No sign of sepsis in middle or internal ear. The rabbit suffered temporary loss of weight but survived entire experimental period (52 weeks). H. & E. × 190.

commencing new bone formation was visible in one of the semicircular canals (Fig. 10). In 3 of the animals with labyrinthine lesions, no evidence of purulent inflammation was found in the middle ear and no histologic signs of a labyrinthine lesion secondary to a previous more active otitis media could be detected. The findings indicated in these animals a primary radiation lesion of the internal ear, and recent haemorrhages and the abundant iron pigment suggested a primary vascular lesion.

No lesions of the labyrinth were apparent in the 2 100 r group.

Comparison between the signs and the site of morphologic changes. The correlation between the signs and the extent of the lesions in the hemispheres and the basal ganglia was poor. Advanced lesions were evident, above all in the centrum ovale, but had not produced any clinical signs. The correlation between the occurrence of vestibulo-cerebellar signs and lesions in the cerebellum, pons and pons nerves, and the ears, is discussed below.

The rabbits with vestibulo-cerebellar signs are analysed in Table 3, which also gives the sites of the lesions.

In the 3 000 r group the vestibulo-cerebellar signs were combined with labyrinthine lesions in 3 animals, but all of the animals in this group had cerebellar lesions to a varying extent. In 2 rabbits only cerebellar lesions seemed to be responsible for the signs, but the possibility of neural damage cannot be excluded since the nerves were not studied in serial sections.

In the 10 500 r group the vestibulo-cerebellar signs were associated with morphologic labyrinthine injury in 6 of the animals, and in one of them the auditory nerve also was damaged. In none of these animals was any cerebellar lesion demonstrable. Two rabbits in the 10 500 r group had limited cerebellar lesions; in one the head was tilted but the other presented no signs. It is thus clear that the vestibulo-cerebellar signs in this group were largely due to peripheral radiation lesions of the labyrinth and/or pons nerves.

Table 3

Vestibulo-cerebellar signs and location of lesions

	Type of treatment:	3 000 r (single)	2 100 r (single)	10 500 r/30 days
Signs:	Vestibulo-cerebellar signs	9 animals	—	8 animals
Site of lesions	Corpora quadrigem.	2 animals	1 animal	—
	Cerebellum	All »	—	2 animals
	Pons or roots of pons nerves	5 »	—	—
	Periphery of pons nerves	4 »	—	2 animals
	Labyrinth:			
	Aseptic	1 »	—	5 »
	Purulent	2 »	—	1 »
	Middle ear:			
	Fibrosis + osteitis	All »	—	7 »
	Ditto + purulent inflammation	3 »	—	4 »
	Teeth:			
	Oblique bite	6 »	—	—

A few animals with turning of the head had very small cerebellar lesions and no changes in the pons nerves or labyrinths. It is possible that processes in the neck musculature or its insertions might have been responsible for this sign (Fig. 4). Oblique wearing down of the teeth was evident in 6 animals of the 3 000 r group and lesions of pons nerves were demonstrated in 4. A lesion of the trigeminal nerve was observed in one animal; this nerve was studied in a few cases only and might have been damaged in more rabbits.

Comments. Four of the animals in the group that received a single dose of 2 500 r had vestibular signs. In 3 of them these could be explained by changes observed in the pons or cerebellum. The fourth had probably sustained peripheral neural damage. Five of the animals in the 6 500 r/12 days group presented vestibulo-cerebellar signs that were often marked. Only in one of the animals could histologic changes be detected in the cerebellum to explain the signs and in 4 peripheral damage may be assumed. A limited peripheral lesion might have been responsible for transient tilting of the head in one of the animals that received a dosage of 8 000 r/30 days.

Discussion

As mentioned in the review of the literature, several investigators have shown that high roentgen doses produce characteristic vestibular signs. THIELE[ANN] stated that these were caused mainly by vascular damage with punctate hemorrhages in the vestibular part of the ear as well as in the eighth nerve.

It is evident from the present investigation that marked vestibular lesions and changes in the nerves of the pons occur after a single dose as well after a fractionated dose and that these produce characteristic signs. The interval be-

Table 4

quency of vestibulo-cerebellar signs and lesions following various doses (10 animals in each group)

Type of treatment:	Single dose (skin)			Fractionation of dose (skin)				
	3 000 r	2 500 r	2 100 r	6 500 r 12 days	5 400 r 12 days	10 500 30 days	8 800 30 days	6 600 30 days
Ve bulo-cerebellar s	9	4	0	5	0	8	1	0
Ve ed lesions in bellum, pons erve roots ...	9	3	0	1	0	2	0	0
La inthine or litory nerve le- s:								
V ified	5	—	0	—	—	6	—	—
S gested	—	1	—	4	—	—	1	—
Total	5	1	0	4	0	6	1	0
Lab inthine dose (10 %)	2 000 r	1 600 r	1 400 r	4 400 r	3 000 r	7 100 r	5 400 r	4 500 r

tween the irradiation and the onset of signs was between 4 months and 1 year and the pathogenesis of the lesions varied. In some cases the signs could be explained by septic conditions of the middle ear, encroaching upon the internal ear, and were occasionally due to osteogenic sarcoma in this region. Lesions of the pons and cerebellum were also contributory causes.

One group of animals without such complications remains in which the labyrinthine and peripheral neural damage could explain the signs while in another group such an explanation was probable. The morphologic analysis revealed labyrinthine necrosis and in several cases a haemorrhagic component or abundant deposition of iron pigment strongly suggested a vascular origin. Like THIELEMANN, however, we were unable to demonstrate any direct vascular lesion.

It may be concluded that the pathogenesis of certain late radiation lesions of the internal ear is the same as those in the brain, i. e. the vascular changes seem to be primary, especially when the cerebral lesions are discrete (BERG and LINDGREN 1958). At the same time a single haemorrhagic lesion in the labyrinth may cause a transient or permanent labyrinthine syndrome while a corresponding lesion anywhere within a large region of the brain may cause no signs at all.

It would appear that the previous sceptical attitude towards disturbances of function due to damage of the internal ear (EWALD 1905, MARX 1909, CHILOW 192 and others) was not justified. Differences in the irradiation technique and the duration of observation period may explain the discrepancies in the histologic appearances reported.

Close analysis of the time-dose relationship was not possible if only verified 'pure' radiation damage of the internal ear was to be considered. Septic lesions

of the internal ear were fairly common following a single dose but after fractionation of the dose the frequency of such complications was low. A focal dose of 7 100 r/30 days was thus found to produce pure radionecrosis in the internal ear in 50 % of the rabbits.

The septic complications are, however, secondary to mesenchymal radiation reactions of the skin, skull and middle ear. Fibrosis, sclerosis, necrosis and atrophy paved the way for infection. There may therefore be justification for considering lesions of the internal ear irrespective of their pathogenesis.

The frequency of all lesions in the different groups of animals and their relation to the focal doses are given in Table 4 from which is evident that the tolerance doses, i. e. the largest focal doses producing no signs nor morphologic damage to the internal ear, were: 1 400 r single dose, 3 000 r/12 days and 4 500 r/30 days. For comparison it might be mentioned that the smallest doses found to produce discrete lesions in the rabbit's brain were: 1 300 to 1 700 r single dose, 3 800 r/12 days and 5 000 r/30 days (BERG and LINDGREN 1958). The radiosensitivity of the internal ear and the brain in rabbits thus seems to be of about the same order.

Limited personal experience with high energy radiation suggests the same conclusion. Co^{60} irradiation of one half of the head of rabbits with a single dose of 2 200 r (to the ear) was found to produce no disturbances of function nor morphologic changes in the ear while the smallest dose to produce morphologic cerebral lesions was 2 300 r. These doses correspond to about 1 750 r at 200 kV roentgen (RBE = 0.75, BERG and LINDGREN 1959).

SUMMARY

Vestibulo-cerebellar signs and morphologic changes in the ear of the rabbit were observed following roentgen irradiation (200 kV) of half the brain. A single dose of 2 500 r or more complicated the histologic appearances by producing septic lesions in the middle ear and labyrinth. After fractionated irradiation such complications were rare but radionecrosis apparently caused by primary vascular lesions was evident in the labyrinth.

ZUSAMMENFASSUNG

Vestibulo-zerebelläre Symptome und morphologische Veränderungen traten im Ohr von Kaninchen nach Röntgenbestrahlung (200 kV) der einen Hirnhälfte auf. Bei Einzeitbestrahlung mit 2 500 r oder mehr war das histologische Bild oft durch septische Veränderungen im Mittelohr und im Labyrinth kompliziert. Nach Fraktionierung der Bestrahlung waren derartige Komplikationen selten; man fand jedoch reine Radionekrosen im Labyrinth, welche offenbar durch primäre Gefässchädigung entstanden sind.

RÉSUMÉ

Les auteurs ont observé des symptomes vestibulo-cérébelleux et des modifications morphologiques sur l'oreille de lapins ayant subi une irradiation roentgen (200 kV) de la moitié du cerveau. Après une dose unique de 2 500 r ou plus, les aspects histologiques sont compliqués

par les lésions infectieuses de l'oreille moyenne et du labyrinthe. Après une irradiation fractionnée, de telles complications sont rares, mais le labyrinthe présente une radionécrose, apparemment due à des lésions vasculaires primitives.

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BOOK REVIEW

MEDICAL PHYSICS. Volume III. Edited by Otto Glasser. 754 pages, 595 illustrations. The Year Book Publishers, Chicago 1960. $ 25.

Since the first two volumes of this standard work appeared in 1944 and 1950 the field covered has been rapidly expanding. The increasing need which has long been felt for a treatment of recent developments has now been fully met by the third volume.

Many articles are new but others are supplementary to articles in the earlier volumes. When nothing fresh had to be added, only the title of the earlier article and a reference have been entered; to take full advantage of the new volume, the two earlier volumes should therefore be available. No less than four different, alphabetic and systematical indices to the complete series facilitate the finding of any desired information and greatly enhance the usefulness of the new volume.

The book is an exclusively North American production, 180 of the 181 authors being residents of the U. S. A. and one of Canada. A European reader would hardly class some of the papers, e. g. on anesthesia, heart operations, hay fever, and hypodermic needles, as medical physics.

An idea of the scope of the work may be conveyed by giving some of the headings of the articles — Application of control system theory in biology; Computers (analog and digital); Information theory in biology; Radioactive isotopes (several articles); Automatic microscopy; Servoanalysis of pupil reflex to light; Space medicine. Some of the papers, especially the more theoretical ones, may be rather difficult for the average reader to understand but a study of the introductory literature which is quoted together with references to the more advanced literature, will prove helpful.

Among articles of special interest to readers of this journal are those on radiotherapy, dosimetry, biologic effects of radiation, radiation protection, radioisotopes, autoradiography, accelerators, roentgen diagnostic methods, and image intensifiers. It is only in this field that the reviewer can express any opinions on the completeness and correctness of the information given, and with few exceptions, such as on the article on ionization (p. 497—499), they are very favourable. It seems a pity that the table of radioisotopes in Volume II (in which the isotopes were grouped according to methods of production) has not now been supplemented with fresh data and the isotopes arranged in the order of atomic numbers instead. These are minor criticisms, however, and do not detract from the great value of the book.

Sven Börner